KREFTFORENINGEN

The Intervention Centre

Oslo University Hospital - Rikshospitalet

Oslo, Norway

NEW MINIMALLY INVASIVE TECHNIQUES IN THE TREATMENT OF PATIENTS WITH LESIONS IN THE LIVER: LAPAROSCOPY AND EXTRACORPOREAL HIGH INTENSITY FOCUSED ULTRASOUND

Airazat M. Kazaryan

Doctoral Thesis

Faculty of Medicine, University of Oslo

Oslo, Norway

2013

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1575

ISBN 978-82-8264-441-9

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Akademika publishing.
The thesis is produced by Akademika publishing merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Dedicated to the memory of innocent victims of crimes against humanity and
to the memory of true strugglers for justice, goodness and peace…

Dedikert til minnet om uskyldige ofre for forbrytelser mot menneskeheten og
til minnet om sanne forkjempere for rettferdighet, godhet og fred …

Посвящается памяти невинных жертв преступлений против человечества и
памяти истинных борцов за справедливость, добродетель и мир...

Նվիրվում է մարդկության դեմ հանցագործությունների անմեղ զոհերի եւ արդարության,
առաքինության ու խաղաղության նվիրյալ մարտիկների հիշատակին...

Dedicated to the memory of untimely
gone relatives and friends...

Dedikert til minnet om for tidlige
tapte slektninger og venner...

Посвящается памяти безвременно
ушедших близких и друзей...

Նվիրվում է վաղաժամ հեռացած հարազատների
եւ ընկերների հիշատակին...

Contents

Page

1. ACKNOWLEDGEMENTS

In this section of the thesis the author has unique occasion to express his personal gratitude, feelings and thoughts. And I take this mission with a major ardour!

This thesis is the product of continuous efforts of many wonderful individuals. The author feels great honour to be able to use this opportunity to acknowledge their contributions. Francis Scott Fitzgerald wrote: “You don't write because you want to say something, you write because you have something to say”. These words are applicable to both fiction and scientific publishing. In my adolescence I felt this personally to be true in books of various writers; in particular I would like to mention the books of Franz Werfel, Levon Zaven Sourmelian, Siamanto, William Saroyan, Francis Scott Fitzgerald and Jack London (it is obvious that every person has their own favourite list). I do hope that readers of this thesis will feel that our work has “something worth saying”…

The present work was carried out during 2007-2013 at the Intervention Centre and the Surgical Department, the Oslo University Hospital, Rikshospitalet. The research project was supported by the Norwegian Cancer Society (Kreftforeningen), which I am very thankful to.

First, I express my deepest gratitude to my main supervisor and friend Prof. Bjørn Edwin, MD, PhD. His surgical charisma, research bravery, huge immutable enthusiasm and great knowledge have enabled the studies described in this thesis to be performed. I would also like to mention his early inspirational introduction of me to a bright world of minimally invasive surgery and mentoring me in my first steps as a young exchange student in Oslo in 1999-2000. It was the start of a journey into a splendid field of medical research and magnificent surgery…

I would like to thank my co-supervisor Prof. Erik Fosse, MD, PhD for his continuous support in the studies and the creation of an excellent multi-specialty research team at the Intervention Centre that is eager to promote and introduce research achievements in clinical practice. He nicely combines different public highly important roles such as surgeon, researcher, musician and philanthropist. His door has been always open for advice, support or just an informal chat.

I thank my co-supervisor Per Kristian Hol, MD, PhD for his continuous support and opening a world of magnetic resonance based techniques. His optimism during arduous experimental work was extremely inspirational and is highly appreciated.

Many thanks also to my close co-worker Irina Pavlik Marangos, MD, PhD; without her support, enthusiasm and especially industrious and patient registration and analysis of clinical data, one would never have observed such fruitfulness of our research group. Her assistance in animal studies is also highly appreciated.

I am grateful to Tom Mala, MD, PhD for research support, especially in the earlier stages, and for never exhausting interest in our research. Without his help in the preparation of the early application to the Norwegian Cancer Society, the presented thesis could scarcely be a reality.

Bård Røsok, MD, PhD and Arne Rosseland, MD, PhD also deserve special acknowledgment. Their concise topical comments during the study planning and manuscript drafting were very helpful and highly appreciated. Numerous discussions with them on clinical aspects of minimally invasive surgery have greatly contributed in the development of my research intuition within laparoscopic surgery.

I would like to thank my close senior collaborators in the clinical part of this study: Olaug Villanger, MD, PhD and Øystein Mathisen, MD, PhD. Their contributions were very valuable for carrying out these studies.

Many thanks also to Ivar P. Gladhaug, MD, PhD, Karl-Erik Giercksky, MD, PhD and Pål-Dag Line MD, PhD for their interest and support in the clinical studies.

I am very thankful to Åsmund A. Fretland, MD who picked up with pleasure the PhD baton of the minimally invasive liver research at the Oslo University Hospital. I am thrilled to observe the enthusiastic research start of Sven-Petter Haugvik, MD, Nadya Postriganova, MS and Leonid Barkhatov, MD. Our group is now convinced to move further forward in minimally invasive surgical research with such bright replenishment.

Many thanks to Bjørn Atle Bjørnbeth, MD, PhD, Trond Buanes, MD, PhD, Anne Waage, MD, PhD, Knut Jørgen Labori, MD, PhD and many others, including those already named, for promoting continuous laparoscopic liver research and the Oslo COMET-study in particular.

I am thankful to Frederic Courivaud, PhD for introducing me to magnetic resonance physics, which was crucial for carrying out an experimental part of this thesis. His thoroughness, persistence and ardour in the analysis of research data have been very impressive and are highly appreciated.

Many thanks to Alice Lund, MD for her histopathologic expertise, which contributed greatly to the study of experimental HIFU liver ablation. I am also grateful to Per Steiner Halvorsen, MD, PhD and Petter Jebsen MD, PhD for their excellent support during the experimental part of this thesis.

I am thankful to radiologic nurses Terje Tillung and Grethe Løvland for considerable technical support in the experimental HIFU studies.

I express my gratitude to the anaesthesia and operative nurses at the Intervention Centre for their excellence assistance during animal experiments – Brita Thorsen Noorland, Kjersti Wendt, Carmen Louwerens, Jenifer Tamson Alcoriza and Linda Engvik.

Many thanks to Ole Jacob Elle, PhD for his exceptional responsiveness to questions and research initiatives related to medical engineering. His dedication to research, observed during numerous late evenings, Saturdays and Sundays spent at the working desk, are highly impressive.

Special credits should be expressed to Marianne Berg for her excellent administrative support during the present study. Her deep knowledge of administrative and procedural issues and ever-readiness to solve obstacles has enabled the significant acceleration of the academic activities at the Intervention Centre.

Prof. Frode Lærum MD, PhD and Julia Ferkis deserve special acknowledgment. Without their sincerest concerns, care and support for the development of medicine and medical science in areas of its need, particularly in Russia, many research projects, including the present study, would never have come to life. I am also very grateful to Prof. Jan L. Svennevig, MD, PhD for his kindness and for mentoring me in the basics of medical research during my early student years in Oslo.

I would also like to use this opportunity to express my gratefulness to many other individuals in the Oslo University Hospital and collaborating institutions for their collaborative research activities resulted in fine research outside of this thesis.

I am delighted to express his gratitude to the staff of the Surgical Department, Sykehuset Telemark health trust for their encouragement and support to my research initiative as well as for favouring of my work on this thesis.

I am in debt to my mother university I. M. Sechenov Moscow Medical Academy, which has educated me as a doctor. I thank Prof. Sergei Grachev, MD, PhD and Associate Prof. Ludmila Mikheeva, MD, PhD for their contribution to the popularisation of medical science, which inspirited me as well, and for providing opportunities for my development as a researcher.

Many thanks to Alexander Alaverdyan, MD, PhD for his support and belief in me.

I feel it necessary to thank Prof. Alexander Shulutko MD, PhD and Prof. Nikolai Kuznetsov MD, PhD for their contributions to my development as a young doctor and researcher. I would like to show appreciation to my close colleagues from Moscow - Grigorii Anchikov, MD, PhD, Vadim Agadzhanov, MD, PhD, Elkhan Osmanov, MD, PhD and Dmitry Beltsevich, MD, PhD.

The author would like to express his acknowledgment to the referees, Prof. John Primrose, MD, PhD, Prof. Roberto Troisi, MD, PhD, and Assoc. Prof. Ola Reiertsen, MD, PhD, who dedicated their valuable time to evaluate the present doctoral thesis.

I was born in Yerevan, an ancient city and the capital of Armenia. As a representative of a nation which survived the genocide of 1915-1923 and narrowly escaped total extermination by the Turkish authorities in beginning of the 20th century, I heard from early childhood the name of a great Norwegian, Nobel Peace Prize laureate and League of Nations commissioner for refugees Prof. Fridtjof Nansen (1861-1930), an indefatigable fighter for humanity, and a great friend of the Armenian nation. He was a great discoverer, he was a prominent scientist, but he was an even greater human. As his daughter Liv Nansen Høyer wrote in a biographic book to Fridtjof Nansen: “The father did not leave care for the Armenian people until the end of his life.” His name will forever live in the heart of every Armenian…

Another great (but less publicly known) Norwegian name lives in the hearts of all Armenians: Bodil Katharine Biørn (1871–1960). Working at a missionary hospital in the Armenian city Mush (in East Turkey in present) in 1915, she was an eyewitness of the massacre of the Armenian, Assyrian and Greek population of Turkey. This horror changed her whole life, to the extent that she devoted the rest of her life to helping survivors of the Armenian Genocide. Her numerous public lectures were aimed to constrain Turkey to acknowledge the crimes committed against humanity with the help of West European press. She became a mother to thousands of orphans – survivors of Armenian Genocide.

The Turkish authorities have succeeded in sweeping off Turkey from Armenian, Assyrian and Greek population - the country’s native inhabitants, who had lived in that land for thousands of years. That meant nearly the end for the ancient Assyrian nation which was even more unlucky than Armenians and Greeks. They have been totally forgotten by the world community and have not received a chance to restore own country after the millennial foreign yoke.

The Turkish authorities have also succeeded to deny their crimes against humanities and continue the cultural genocide after committing the physical genocide. It is presented by both continuous destruction of ancient Armenian historical sites and landmarks and falsification of Turkish origin of ancient Armenians relics. There is absolutely no talk about repatriation of the descendants of the survivors of

the Armenian Genocide or compensation. This policy unfortunately continues to this day, due to total impunity of the past committed crimes against humanity.

As early as at the beginning of the 20th century Prof. Raphael Lemkin (1900–1959), a prominent lawyer and a great humanist, warned that namely the impunity of the committed crimes against humanity and the ignorance of such flagrant tragic event by the world community would be an “inspiration” for repetition of such crimes. As an example, having exterminated 1.5 millions Armenians during 1915, the Turkey authorities have never regretted for it; opposite the impunity and ignorance by the world community instigated the Turkish authorities to continue the Armenian Genocide during the Turkish intervention to Transcaucasia in 1917-1920 and after taking control of Greek territory in West Anatolia following a victory in the Greek-Turkish war 1919-1922.

Two subsequent major genocides of the 20th century, the Jewish Genocide (Holocaust) in the Nazi controlled European countries and the Tutsi Genocide in Rwanda, are two other classical examples of the lessons unlearned by the world community. Adolf Hitler maliciously pronounced in 1939: ”Who, after all, speaks today of the annihilation of the Armenians?”. This was his “excuse” for his deed of horror on the threshold of the Jewish Genocide.

This unconcern undoubtedly attributes to the economic and political factors which still often dominate over humanistic ones in the contemporary community... While unwanted regimes have been easily smashed; little has been done to prosecute the real genocide organizers: Pol Pot, the main organizer of the Cambodian Genocide, was never arrested and spent quietly his 20 years after organizing of massacre of the millions of people. Talaat Pasha, Enver Pasha and Djemal Pasha, the main organizers of the Armenian Genocide, were reburied with Turkish state solemnities at the Pantheon (Hürriyet-i Ebediye Tepesi) of Şişli cemetery in Istanbul...

When in 1999, as a medical student in Moscow, I learnt that I would study in Norway, the most I knew about this country was that it was the land of Fridtjof Nansen. Later I learned many other things about this wonderful country. Norway became a third homeland for me (after Armenia and Russia). I would like to express my gratitude to this country and its kind and cheerful nation that has provided me with many opportunities, among them an opportunity to fulfil this doctoral thesis.

I express my deep gratitude to my grandfathers Assoc. Prof. Hairazat (Airazat) G. Kazaryan, MD, PhD and Ashot A. Hasratyan, grandmothers Serik H. Vanuni, MD, PhD and Seda H. Aghavelyan, to my parents Prof. Mishik A. Kazaryan, PhD and Prof. Arpik A. Hasratyan (Asratian), MD, PhD and my sister Serine M. Kazaryan, MD, PhD for their wholesome influence on me, which, in particular, led me to become a doctor and researcher. Special thanks to my nephew Mikael and niece Ani just for their presence.

I am also very thankful to my friends and relatives for their never-extinguishing support.

Finally, last but not least, I express my very special thanks to my wife Liana Harutyunyan (Arutyunyan) for her love and support, as well as for her tolerance with me throughout my irregular working hours.

Oslo, May 2013 Airazat M. Kazaryan

2: LIST OF PAPERS

Paper I. **Kazaryan AM**, Marangos IP, Rosseland AR, Røsok BI, Mala T, Villanger O, Mathisen Ø, Giercksky K.E, Edwin B. Laparoscopic liver resection for malignant and benign lesions: 10 year Norwegian single centre experience. *Arch Surg.* 2010; 144(1): 34-40

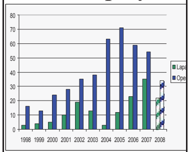
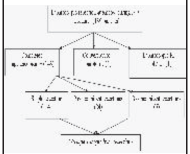
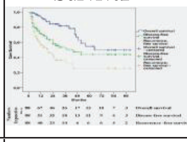
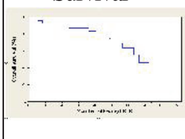
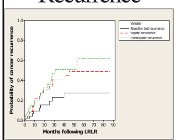
Paper II. **Kazaryan AM**, Marangos IP, Røsok BI, Rosseland AR, Villanger O, Fosse E, Mathisen Ø, Edwin B. Laparoscopic resection of colorectal liver metastases: surgical and long term oncologic outcome. *Ann Surg.* 2010; 251(6): 1005-1012

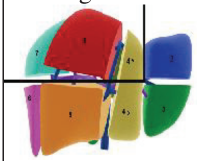
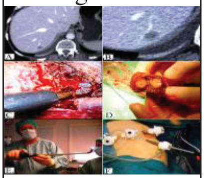
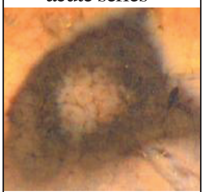
Paper III. Shafaee Z, **Kazaryan AM**, Marvin M, Cannon R, Buell JF, Edwin B, Gayet B. Is Laparoscopic Repeat Hepatectomy Feasible? A Tri-institutional Analysis. *J Am Coll Surg* 2011; 212(2):171-9

Paper IV. **Kazaryan AM**, Røsok BI, Marangos IP, Rosseland AR, Edwin B. Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments. *Surg. Endosc.* 2011; 25(12):3881-9

Paper V. Courivaud F, **Kazaryan AM,** Lund A, Pavlik Marangos I, Jebsen P, Fosse E, Hol PK, Edwin B. Acute and survival studies of magnet resonance guided high intensity focused ultrasound ablation in the swine liver (Submitted to *J Magn Reson Imaging*).

3. THESIS AT A GLANCE

	Questions	Materials / Methods	Results		Conclusion
I	Can a laparoscopic approach provide good outcomes for both benign and malignant liver lesions? Are there benefits of anatomic resections?	139 patients (113 with malignant and 27 with benign lesions), 147 procedures, 176 laparoscopic liver resections. 38 pure anatomic resections and 102 pure non-anatomic resections.	Conversions - 3.4%, blood loss 200 and 400 ml, operative time 148 and 180 min, respectively, for benign and malignant lesions. Blood loss 300 and 350 ml, operative time 185 and 145 min, respectively for benign and malignant lesions. Intraoperative incidents - 7%, postoperative complications - 14.3 % (similar in all subgroups). Postoperative stay - 3 days. Mortality - 0.7%.	Procedures per year  Procedure flowchart 	In experienced hands, laparoscopic liver resection is a favourable alternative to open resection. Perioperative morbidity and mortality appear to be comparable to those of open resections. Anatomic resections are not associated with any benefits.
II	Does laparoscopic liver resection for colorectal liver metastases provide good oncologic outcomes?	107 patients, 118 procedures, 146 laparoscopic liver resections. Mean Fong score - 1.8. Mean Basingstoke Predictive index (BPI) - 7.	Conversions - 4.2%, blood loss - 300 ml, operative time - 188 min. R_0 resection - 93%. Postoperative complications - 14%. 5 year survival - 51% (10% and 7% over the values calculated from Fong score and BPI respectively)	Patient Postoperative flowchart  Survival 	Oncologic outcome including long-term survival is comparable to or better than that of open surgery; the observed actuarial survival is better than expected by Fong's BPI scoring systems.
III	Is laparoscopic approach an appropriate method for repeat liver resection?	76 laparoscopic repeated liver resections were attempted. Operative indications were metastasis (63), hepatocellular carcinoma (3), and benign tumours (10).	Conversions - 11%, blood loss - 300 ml, operative time - 180 min. R_0 resection - 92%. Postoperative complications - 26%, including 8% of major complications. 5 year survival - 55%	Survival  Recurrence 	Laparoscopic approach to repeat liver resection is feasible, safe, and oncologically adequate.

	Questions	Materials / Methods	Results		Conclusion
IV	Does laparoscopic liver resection for posterosuperior segments provide similarly good outcomes like for anterolateral segments?	75 patients who underwent primary minor single liver resection for malignant tumours affecting either posterosuperior segments (1, 7, 8, 4a; group 1) or anterolateral segments (2, 3, 5, 6, and 4b; group 2).	Perioperative and oncologic outcome did not differ between the groups: Operative time - 127 min, blood loss - 200 min, postoperative hospital stay - 2 days. R_0 resection - 95%. Resection margin was the only parameter that differed significantly between the studied groups (median 3 versus 8 mm).	Review of liver segments  Approach to segment 8 	Appropriate adjustment of surgical techniques, equipment and patient positioning enables safe and effective laparoscopic resections for lesions located in both posterosuperior and anterolateral segments.
V	Can extracorporeal MR guided HIFU system provide precise, and safe ablation of the liver resulting in irreversible tissue damage?	13 Norwegian local swine (25-45 kg) were used for research analysis. 7 swine – HIFU-ablation in acute experiment, 6 swine – HIFU ablation in survival experiment (survived 1 week after HIFU-ablation). Applied power 120-350 W.	There was good correlation between the zone of planned ablation, radiologic and histopathologic findings. Histopathology confirmed only minor reversible alterations in acute series. Survival series revealed higher degree of histopathologic alterations, nevertheless only multi-cycle regime with power of 350W resulted in coagulative necrosis of the liver tissue. The latter regime resulted in larger ablation volume than planned due to observed cavitation.	Experimental swine  Macroscopic picture after ablation in acute series  Coagulative necrosis 	MR-guided HIFU ablation in the liver is a challenging ablation modality due to the high vascularity of liver parenchyma. Upon application of high energy protocol (350 W), it is feasible to achieve complete ablation of liver tissue verified by structural histopathology. Impact of multi-cycle protocol, issues of functional analysis of irreversible tissue damage and threshold to cavitation onset require further studies in order to optimise HIFU ablation of the liver.

4. INTRODUCTION

"When the liver is wounded, much blood comes out"

Ambrose Pare[1]

4.1 Open liver resection

One may go back centuries to spot critical developments in the history of medicine that prompted the birth and development of liver surgery. The history of liver surgery can be divided into four periods.[2,3]

During the first period, from ancient times until end of the 19th century, liver anatomy was the main area of concern. The legend of Prometheus, written by Hesoid (750–700 BC), recounts ancient times.[4] Prometheus stole fire from Zeus, the godfather of ancient Greece, and gave it to human beings. For this violation, Zeus chained him to a rock and sent an eagle to devour his liver (Illustration 1). The liver regenerated and grew back to its normal size overnight. Each morning the hungry eagle returned, and Prometheus was captured in perpetual pain. Nowadays the astonishing regenerative capacity of the liver is no longer an inspiration for mythical tales, but is the basis for contemporary liver surgery.

Illustration 1: Detail from Prometheus Bound, by Peter Paul Rubens, 1612–8, the Philadelphia Museum of Art.

The Ancient Egyptian physician Herophilus from Alexandria (330–280 BC) was one of the first anatomists who described the liver, although his written work no longer remains. The Greek physician Galen (AD 130–200) referred to his work and described the lobar anatomy and vasculature, interpreting the liver as the source of blood. However, in the subsequent centuries of the Middle Ages, knowledge on liver anatomy moved forward very little.

In the 17th century, anatomists started exploring hepatic anatomy with bright ideas. In 1654, the English physician Glisson cooked the liver, removed the liver parenchyma, and explored the hepatic blood flow with dye (illustration 2).[5] He described the intrahepatic anatomy and topography of the vasculature. Glisson's work was forgotten for over 200 years. Later, in the late 19th century, several authors published studies on liver anatomy, all built on Glisson's publications.[6] In 1888, the German physician Hugo Rex and in 1897, the English physician James Cantlie challenged the accepted anatomic division of the liver.[7,8] They proposed a division line drawn from the top of the gallbladder and back towards the caval vein.

Illustration 2: Intrahepatic vasculature (From Glisson F. Anatomia hepatis. London: Dugard; 1654).

The growing understanding of liver anatomy was one of the substantial prerequisites for the development of liver surgery. However, it was still far from realisation, and the liver remained a fragile bleeding mystery. Only anecdotal records of liver surgery existed; these were typically reports about the removal of protruding liver tissue after injury. Among the reporting surgeons were Ambroise Pare from France, J.C. Massie from USA, and Victor von Bruns from Germany.[9] However, hepatic trauma at that time was generally managed without surgery.

The second period lasted from the end of the 19th century to the 1940s. In the 19th century, two fundamental concepts enabling major surgery were introduced: anaesthesia and asepsis. In 1842, Crawford W. Long used ether as a surgical anaesthetic for the first time in the USA. In 1867, Joseph Lister from Scotland introduced antiseptic techniques against bacterial infections after Louis Pasteur from France had discovered the dangers of bacteria.

This was the time of the first successful resections. Liver resections were performed and reported in many centres around the world. However, the outcomes were too dismal and complications following the use of mattress sutures were too high. Resections could not be performed any other way, however, without any tools to visualise the liver, and without blood banks and intensive care units. Carl Langenbuch, from Germany, performed the first cholecystectomy; he reported the first elective and successful liver resection in 1888.[10] In 1891, William W. Keen from the USA performed the first resection in the USA.[9] He used the ‘‘finger fracture’’ technique to divide the liver parenchyma. However, intraoperative bleeding control remained the most striking challenge. In 1896, Michel Kousnetzoff and Jules Pensky suggested the use of a continuous mattress suture above the resection line for controlling bleeding.[11] In 1908, Pringle from Scotland, described a method using temporary compression of the portal ligament.[12]

It was once more the excellent work of anatomists that provided the key insights to overcome major bleeding. In 1888, Hugo Rex, from Germany, and in 1897, James Cantlie, from England, challenged the established approach to anatomic division of the liver by the falciform ligament.[7,8] They separated the liver by the branches of the portal vein in corrosion studies. Also, they defined an avascular plane through the gallbladder bed toward the vena cava and through the right axis of the caudate lobe along the middle hepatic vein. At present, this plane is known as the Rex-Cantlie line. At the beginning of the twentieth century, Walter Wendell, from Germany, and Hansvon Haberer, from Austria, were the first surgeons to perform resections along this anatomic plane.[13,14]

The third period lasted from the 1940s to the mid-1990s. The experience which had been gained during World War II had a huge initial impact on the further development of liver surgery; however, the development of anaesthesiology, imaging and safe surgical techniques essentially contributed to this development.

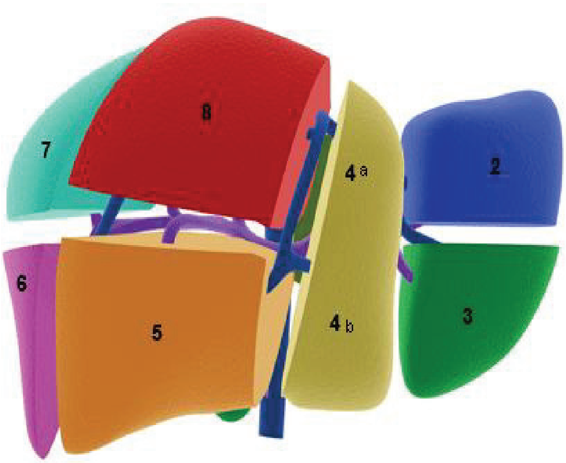
Essentially due to the work of the French surgeon and anatomist Claude Couinaud, the anatomy of the liver has become clearer.[15-17] He studied the anatomy by means of casting the vascular and biliary structures of the liver. Couinaud finally defined liver anatomy from the vascular structures serving each area of the organ. His suggestion of dividing the liver into eight segments according to the portal vein and venous branching is the segment definition that most liver surgeons use today (Illustration 3).[18]

The first planned pure anatomic liver resection is credited to Lortat-Jacob, who performed a right lobectomy as treatment for metastatic colon cancer in 1952.[19,20]

Several factors combined to allow the resurgence of operations on the liver that began around 1950. First, the lessons of World War II in handling liver trauma increased our confidence in the control of bleeding. Second, more attention was paid to inflow and outflow control, with the specific ligation of vessels gradually replacing grosser techniques as a result of the work of Couinaud, Hjortsjo, Goldsmith, Woodburne, Healey and colleagues.[15,16,21-23] Third, the ability to carry a patient through a difficult operation increased exponentially with advances in metabolic, haemodynamic, and respiratory support. Fourth, liver imaging has undergone major improvements in the last 30 years. Finally, Hugh Edmondson determined the pathology of these rare tumours by collecting cases from many sources.[24]

Due to careful attention paid to biliary and especially vascular anatomy of the inflow and outflow tracts, major liver resections came to have acceptable morbidity and mortality levels and were, therefore, often used. The total number of liver resections increased dramatically during those years.

Illustration 3: Liver segments, frontal view.



The fourth and present period started from the mid-1990s. This period was impacted by tremendous progress in surgical and especially laparoscopic instrumentation[25] and the concept of multimodal treatment.[26]

This period is characterised by: 1) The popularisation of parenchyma-sparing techniques, which became possible due to the introduction of principally new surgical instrumentation based on ultrasound, coagulation and stapling principles enabling the provision of safe non-anatomic parenchyma-sparing multiple resections instead of major resections;[27,28] 2) The increased application of minimally invasive modalities: laparoscopic surgery and ablative modalities;[29] 3) The wide application of adjuvant and neoadjuvant chemotherapy with regard to colorectal liver metastases;[30] and 4) Spreading of unilateral embolisation or ligation of the portal vein inducing hypertrophy of the future liver remnant and therefore enabling the resection of many borderline liver tumours.[31]

The indications for surgery in liver metastases of colorectal cancer and also for hepatocellular cancer and cholangiocarcinoma have expanded considerably in this period.[32] As the number of liver transplants considerably increased, transplantation became a competitor to liver resection in regard to hepatocellular cancer and cholangiocarcinoma.[33]

4.2 Minimally invasive techniques

<u>Birth of laparoscopic liver resection</u>

In the beginning of the 1980s, Kurt Semm from Germany performed the first laparoscopic appendectomy[34], and in the mid-1980s, Eric Mühe from Germany and Philippe Mouret from France reported pilot cases of laparoscopic and videolaparoscopic cholecystectomy, respectively[35,36]. The introduction of these procedures announced a revolution in gastrointestinal surgery. In 1991, Harry Reich and colleagues from the USA, and, in 1992, Michel Gagner and colleagues from Canada/USA reported the first cases of laparoscopic liver resection.[37,38] At that time, Gagner's report was only considered as a poster presentation at the congress of the Society of American Gastrointestinal Endoscopic Surgeons; since that time, the feasibility and safety of this procedure have been documented in several reports.[27,39-53] However, in contrast to the general surgery, the advancement of laparoscopic surgery was not so swift in regard to liver surgery, especially concerning malign lesions.[54]

In spite of the apparent progress of laparoscopic hepatobiliary surgery, many hepatobiliary surgeons are still very cautious in regard to the wide application of these advanced techniques.[55] It relates to poor knowledge about long-term outcomes of such procedures as well as to challenges which have been met by surgeons as a way of mastering this technique.[55]

Recently, several technological solutions have been suggested to decrease the technical challenges of the laparoscopic approach and enable its easier introduction in centres lacking surgeons with exceptional laparoscopic technical skills, i.e. promoting the rapid introduction of laparoscopic techniques at ordinary departments of hepatopancreatobiliary surgery worldwide. Robotic assistance and on-line image guidance based on the three-dimensional reconstruction of preoperative imaging presents typical examples of such modalities.[56-59] However, the role of these innovations are still disputable.

Topical problems

In Norway, the most frequent liver neoplasms evaluated for surgical treatment are colorectal metastases.[60] Surgical resection has so far been considered the only treatment to offer prolonged survival to patients with primary or metastatic cancer confined to the liver.[61] Patients suitable for hepatic resection have shown quite good 5-year survival rates after operation, ranging from 30% to 55%.[62-64]

The well-established open approach is associated with high surgical trauma.[65] The introduction of laparoscopic liver resection has been taken with high expectations.[53,66,67] The attraction of laparoscopic liver resection is that it has the potential for more rapid recovery from surgical trauma. This results in a shorter hospital stay, less postoperative pain, less postoperative morbidity, an earlier return to normal activities, and economic benefits compared to the open approach.[68,69] Use of the laparoscopic technique has been reported for a range of liver disorders; this technique even played a role in harvesting of the living donor liver for transplantation.[70,71] This technique has also been used in an increasing proportion of patients in leading institutions. If in earlier years the laparoscopic approach was mainly considered for minor wedge liver resection,[72] all types of liver resections are currently reported and in expert centres indications to laparoscopic liver resection is largely the same as to open liver resection (except very bulky tumours and necessity for vessel/bile duct reconstruction).[73]

However, patients operated on for malignant liver lesions represent special concerns, such as the uncertainty of oncological outcomes. Preliminary studies in laparoscopic surgery suggest the feasibility of the achievement of similar levels of oncological radicalism.[74] There are poor data in regard to late oncological outcomes of laparoscopic liver resection.[75,76]

Repeat liver resections due to tumour recurrence has been proven to be an effective treatment option.[77,78] Its aspects would gain new challenges with the introduction of laparoscopic techniques. This may be expected due to the lower occurrence of adhesion development after the laparoscopic procedure,[79] which would facilitate subsequent repeat liver resection. This could contribute to the better survival of patients with liver malignancies.

Laparoscopic resection for easily accessible superficial liver segments have been relatively rapidly adapted in clinical routine in many hepatopancreatobiliary centres worldwide.[80] However, it has been a discord in surgeons' opinions on the approach to liver segments that are laparoscopically difficult accessible and challenging (the so-called posteriosuperior segments). The accumulation of experience and the introduction of new surgical armamentarium appears to resolve this problem.[81,82]

The volume of necessary resection was very disputable in the era of open surgery;[28,83] the introduction of laparoscopic techniques has added a new focus on this topic due to the new paradigm of operative tactics. A steady tendency to parenchyma-sparing resections observed in the last decade will go through the trial in laparoscopic epoch.[84]

Some problems still remain regarding the final preoperative diagnosis of liver lesions in spite of the enormous progress of both imaging modalities and tumour marker research.[85,86] In particular, small tumours of the liver or bile ducts still represent a clinical challenge, though the detection rate of these tumours by radiological and other methods has essentially improved. Medicine is not perfect at distinguishing intrabiliary malignancies from benign strictures, and this enigma has not been resolved by years of experience with intrabiliary endoscopy, computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).[87] Fine-needle aspiration biopsy has been largely abandoned due to the unacceptable rate of tumour dissemination.[88]

In the past, mistaken preoperative diagnosis has resulted in unnecessary laparotomy and liver resection, which could have considerable consequences for patients. Nowadays, the application of laparoscopic approaches in cases of mistaken preoperative diagnosis of liver disease substantially lessens the negative consequences of such faults.

Research in genetics could potentially contribute to this issue;[89] conceivably, the future will enable asymptomatic benign tumours to be diagnosed with sufficient accuracy to make surgery and ablation superfluous.

Ablative modalities, extracorporeal high intensity focused ultrasound

The majority of patients with hepatic malignancy have disease that is not amenable to surgical resection.[90] This, and a high incidence of new liver metastases following the successful resection of metastases (60%–80%), has spurred interest in therapeutic alternatives. [91]

Image-guided tumour ablation is consigned to a group of treatment methods introduced in the last two decades that have been deemed important tools in the treatment of a wide range of tumours.[92] Malignancies in the liver and kidneys are most often indications for ablative treatment.[93] Among the different options, radiofrequency ablation, laser ablation and cryoablation have gained highest popularity[94-96]. However, these methods are still associated with a high risk of tumour recurrences.

Ultrasound technology has allowed the utilisation of focused ultrasound energy for therapeutic aims such as tissue ablation. High intensity focused ultrasound (HIFU) is a recently introduced ablative modality with growing popularity.[97,98] Distinct to radiofrequency or cryoablation, ultrasound is entirely non-invasive and can be applied to tumours that are deep within the body, provided that there is an acoustic window to enable the transmission of ultrasound energy.

The physical principals of HIFU were first described by Wood and Loomis in 1927.[99] In the middle of the 1930s Lynn and co-workers started the first animal experiments using HIFU to treat liver tumours; however, the absence of visualisation tools at that time limited the development and practical application of HIFU.[100] Interest in HIFU has recently revived together with the establishment of three-dimensional imaging.[101] While ultrasound-guided HIFU ablation of the liver has already been introduced in several centres worldwide,[102-105] the MR-guided HIFU ablation is still performed only in experimental laboratories.[106,107] A reason for that could be challenges due to the more complicated MR equipment required for procedural on-line control.

HIFU with ultrasound has restricted the target definition and monitoring capability of the ablation procedure. Combining MRI with multiple-element phased-array transducers to create

MR-guided focused ultrasound thermal therapy provides more accurate targeting and real-time temperature monitoring.[108] The site and shape of the lesion can be predetermined, each sonication is delivered within a few seconds, and lesions are very sharply defined.[109] HIFU could be potentially performed without general anaesthesia; there is no risk of tumour seeding in needle tracks.[110,111]

Despite the wealth of research in the field of HIFU, its application as a non-invasive surgical tool is still in its infancy. Experimental and clinical research is required to further investigate and improve its safety and efficacy in the treatment of liver malignancies.

5. AIMS OF THE STUDY

General aim:

The main goal of this thesis was to estimate and develop new minimally invasive techniques in the treatment of patients with lesions in the liver: laparoscopy and HIFU.

Specific aims:

- A. Evaluate perioperative outcomes of laparoscopic liver resection based on large volume single centre material.
- B. Evaluate surgical and late oncologic outcomes after laparoscopic liver resection for colorectal metastases.
- C. Evaluate laparoscopic repeat liver resection after laparoscopic or open primary liver resection.
- D. Evaluate laparoscopic liver resection for lesions located in easily and difficult accessible segments.
- E. Establish and develop experimental an *in vivo* swine model for HIFU ablation of the liver.
- F. Evaluate the safety and efficacy of MR-guided HIFU to ablate liver parenchyma in an *in vivo* swine model.

6. MATERIAL

6.1 Patients

Two hundred and twenty patients who underwent laparoscopic liver resection during 244 procedures from August 1998 to December 2010 at the Oslo University Hospital, Rikshospitalet formed the research basis for the clinical section of this thesis.

Clinical data were collected from patient journals and registered in an MS Excel database established in 2000. Subsequently, the database was prospectively updated, except for the period 2005 to 2006 when data were retrieved retrospectively.

Paper 3 also included 47 patients operated upon in partner institutions (31 patients in the Institut Mutualiste Montsouris, Paris, France and 16 patients in the University of Louisville, Louisville, USA).

Protocols for the clinical studies have been approved by the Institutional Patient Ombudsman and the Regional Ethic Committee (Helse Sør-Øst).

6.2 Experimental animals

Thirteen male Norwegian land swine with a median body weight of 31 kg (range 25-45.5 kg), who were treated on the liver by the Sonalleve HIFU system under guidelines of 3 Tesla Achieva MR scanner (Philips Healthcare) from April 2010 to March 2011 at the Intervention Centre, the Oslo University Hospital, Rikshospitalet, formed the research basis for the experimental part of this thesis.

Research data were collected and registered in an MS Excel database.

The protocol for the experimental study was approved by the National Animal Research authority.

.

7 METHODS

7.1 Laparoscopic technique

Pneumoperitoneum was established by an open technique, and intraabdominal carbon dioxide gas pressure was set at 8 to 10 mm Hg. A 30° laparoscope (Olympus, Tokyo, Japan) and 5- and 12-mm trocars (Tyco/Covidien, Norwalk, Connecticut, USA) were used. In very difficult cases (e.g., when the quality of the liver parenchyma prevented adequate mobilisation of the right lobe), a flexible laparoscope (HD EndoEYE LTFVH; Olympus, Tokyo, Japan) was used. The number of trocars depended on the lesion location and the patient's body build, but usually numbered 3 to 5. For lesions located laterally and posteriorly on the right side, the patients were placed in a lateral position with the right abdominal side elevated between 30° and 60°. Patient positioning and trocar placement was carefully adjusted to suit the tumour location and patient constitution.

A diagnostic and staging laparoscopy was performed first. Intraabdominal adhesions due to previous surgeries were treated in most of the patients. The liver was thereafter thoroughly examined using laparoscopic ultrasonography (Hitachi Medical Corp, Aloka Inc, Tokyo and SonoDoppler; Sintef Helse/Mison, Trondheim, Norway) with Doppler function.

The resection line was marked at the liver surface by electrocautery following ultrasonographic examination to locate the tumour. The capsule was divided by use of ultrasound scissors (Autosonics [Tyco/Covidien], SonoSurge [Olympus]), or Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, Ohio, USA).

Parenchymal transection was performed mainly by either an ultrasound surgical aspirator (applied trademarks – SonoSurg Aspirator, CUSA or Selector) or a bipolar coagulator Ligasure. Clips were used for vessel transection. Endo-GIA (US Surgical Corporation, Norwalk) was applied only for transection of major vessels, mainly during formal hemihepatectomies. Ultrasonic scissors were seldom applied for parenchymal transaction.

The resections were guided by repeated ultrasonography for the exact location of the tumour. Meticulous dissection ensured that vessels and bile ducts were safely secured. The Pringle manoeuvre was not applied. During left and right hemihepatectomies, we used extraparenchymal and transparenchymal techniques to divide the hepatic vessels and biliary ducts. Procedures were routinely performed by fully laparoscopic techniques; a hand-assisted technique was applied in very few cases to avoid conversion to open surgery. The resected liver was removed in one piece through an enlarged umbilical port incision, using a 15-mm pouch (Endo Catch; US Surgical Corporation). An abdominal drain was used in only a few cases.

7.2 Standardisation tool for outcome evaluation

Minimally invasive liver surgery has a history of about 20 years; however, up to the mid-2000s only a small proportion of liver surgeries were done laparoscopically.[84]

The Oslo University Hospital is one of the leading centres worldwide in the area of laparoscopic liver surgery, both related to the number of cases, outcomes and relatively early introduction in 1998. Having this starting point we have made a comprehensive review of the existing systems for standardised reporting of surgical outcomes and perioperative morbidity. This was urgent because our study was not intended to be comparative; thus, standardisation was considered as the only way to achieve objective data which would be valid for application by surgeons and researchers from different parts of the world.

Firstly, we have chosen to apply the registration of both intent-to-treat and per protocol outcome. This required only a small amount of extra time, but gave a quite comprehensive picture of surgical outcome. Perioperative adverse events were naturally recorded by the intent-to-treat manner.

Secondly, we have purposefully reviewed a huge number of international papers reporting large surgical materials with a focus on the analysis of perioperative mortality. The simple 3 grade classification of surgical errors developed by Satava in 2005 took our attention as a model for standardisation of intraoperative unfavourable incidents.[112] A classification of postoperative complications originally developed by Clavien, Sanabria and Strasberg in 1992 and later revised by Dindo, Demartines and Clavien in 2004, by Strasberg, Linehan and Hawkins in 2009, and by Porembka, Hall, Hirbe and Strasbergin in 2010 (Clavien-Dindo-Strasberg classification), was chosen to standardise the reporting of postoperative complications.[113-116]

Later on, we developed our own approach to grade perioperative adverse events.[82,117,118] This incorporates our own classification of intraoperative unfavourable incidents based on the Satava principles and the modified Accordion classification (the last version of the Clavien-

Dindo-Strasberg classification).[112,116] Schematic reproduction of the constituents of perioperative adverse events are presented in Illustration 4. Table 1 presents the classification of intraoperative unfavourable events and Table 2 shows the classification of postoperative complications.

Illustration 4: Schematic reproduction of the constituents of perioperative adverse events.

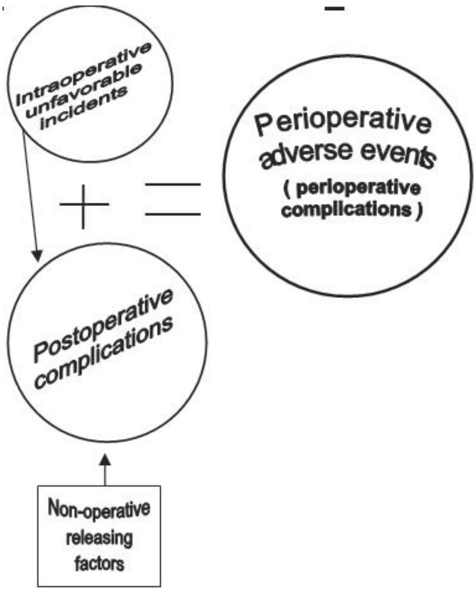


Table 1: Own classification of intraoperative unfavourable incidents elaborated from the Satava approach to grade surgical errors.

Grade	Definition of intraoperative incidents
I	Incidents managed without a change of operative approach and without further consequences for the patient. This includes minor injury of adherent or adjacent organs and minimal changes of intraoperative tactics and cases with blood loss over the normal range.[A]
II	Incidents with further consequences for the patient. This includes cases requiring limited resection of intraoperatively injured organs or cases with blood loss which is appreciably over the normal range.[B] For laparoscopic/thoracoscopic/ endoscopic surgery it includes intraoperative incidents requiring conversion.
III	Incidents leading to significant consequences for the patient.

[A] corresponds to blood loss over 1000 ml in cases of liver resection.

[B] corresponds to blood loss over 2000 ml in cases of liver resection

Table 2: The modified Accordion classification of postoperative complications, the Oslo revision. Text marked by bold italic type presents the modified points in the classification.

Grade[A]	Definition of postoperative complication
I	Requires only minor invasive procedures that can be done at the bedside, such as the insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy are permitted. ***It includes cases requiring a doubly prolonged postoperative stay[B] to treat conditions which are otherwise considered as sequel.***
II	Requires pharmacologic treatment with drugs other than such allowed for minor complications, e.g., antibiotics. ***Postoperative*** blood transfusions and total parenteral nutrition are also included.
III	No general anaesthesia: requires management by an endoscopic, interventional procedure or reoperation without general anaesthesia[D].
IV	General anaesthesia or single-organ failure.
V	General anaesthesia and single organ failure or multisystem organ failure (> 2 organ systems).
VI	Death ***within 30 postoperative days or up to discharge if the patient stays longer in the hospital.***

[A] Minor complications: Grade I-III, Major complications: Grade IV-VI

[B] Median hospital stay for that disease and procedure which is present in the particular institution is to be applied as a reference value.

[C] Need for artificial pulmonary ventilation during patient anaesthesia is a boundary to define general anaesthesia.

[D] Cases when an intervention was performed due to the suspicion of complication (without its confirmation) are not to be regarded as a basis for severity grading. However, such cases should be reported (see examples in the text).

7.3 Experimental HIFU treatment

HIFU Equipment

The Sonalleve MR-HIFU platform from Philips Healthcare integrated to the bed of a 3 Tesla MR Achieva scanner was applied.

Ex vivo porcine models

Prior to animal studies, we had to learn procedures initially on the phantom model and later on an *ex vivo* porcine model. The experience from these procedures was quite inspiring, showing coagulation of muscular tissues.

Illustration 5: Experimental HIFU ablation (fresh porcine ham).

Thus, we were quite optimistic of achieving complete ablation when applying a standard ablation protocol using factory adjustment. In principle, this standard ablation protocol aimed to achieve complete tissue distraction in the target area without injury to neighbouring anatomical structures. However, this protocol was primarily developed for the treatment of uterine fibroids.[119] The applied HIFU system was approved by the European Medicines Agency and the US Food and Drug Administration exactly for this application.

Anaesthesia protocol, animal procedural handling

For experimental studies on the swine model we applied an anaesthesia protocol, which was previously developed in our centre, as a basis.[120] Respiration stops in the position of maximal expiration were necessary to enable HIFU planning, treatment and monitoring. The maximal expiration position may have 2 benefits: it provides some oxygen in the lungs for gas exchange in the early stages of respiration cessation, and it also results in caudal liver displacement, providing lesser coverage of the liver by the ribs. Consequently, a greater liver volume becomes available for safe ablation.

Seven swine were used in non-survival acute experiments and the remaining six animals for the survival experiments. Animals were anaesthetised with Pentobarbital, Isofluran and Morphine.[120] Tracheotomy was applied for the acute series, whereas survival pigs were intubated. A Hickmann catheter was placed in vena jugularis externa in the survival series in order to draw blood samples in the post-procedural period. The skin in the actual region was carefully shaved to facilitate the propagation of ultrasound waves. Animals were transferred to the MR room and placed in prone position with their liver facing the HIFU transducer. Respiration was stopped in expiration for 1-2 min during the MR scanning and HIFU-sonication. Prior to the respiration pauses, the swine were hyperventilated to guarantee adequate oxygenation during respiration pauses.

Animals in the acute series were immediately euthanised after MR post-procedural imaging. The whole liver and abdominal skin samples were resected for histopathology analysis.

Swine in the survival series were awakened and kept alive for a week. After follow-up MRI examination, they were euthanised and their liver/skin samples were resected for histopathological analysis.

Illustration 6: The experimental animal under treatment: A. An anaesthetised swine on the HIFU-treatment table; B. Pig in the MR scanner under treatment.

A.

B.

HIFU protocol

The duration of sonication was 30 to 48s, at a frequency of 1.2 MHz, and with an acoustic power of 120-350 W. The HIFU focal point was automatically adjusted electronically to form an ellipsoid cell of 4x3x10, 8x8x20 or 12x12x30 mm^3, performed individually or in clusters of overlapping cells.[121] The standard sonication protocol implies a test low-energy sonication prior to treatment sonication, which enables the power which is necessary for complete ablation to be calculated based on the temperature rise.

$$\textit{Calculated HIFU-machine suggested power} = \frac{\textit{Required temperature rise X Power X Multiplication}}{\textit{Observed temperature rise}}\ \textit{factor}$$

Multiplication factor was considered to vary from 1 to 2 depending on the type of treatment cells and their size, but the recommendations from the manufacturer were not constant and have been in continuous revision.

The sonication protocol was designed to investigate various characteristics, such as the use of treatment cells with feedback, acoustic power level, multiple sonication cycles (at a single location), and sonication cell agglomeration to clusters. Moreover, some ablations were planned to include blood vessels in order to evaluate their cooling effect on HIFU sonication.

In order to avoid ablation of the major biliary ducts, MR-cholangiography was acquired before sonication. In cases of multiple sonication cycles, the cooling time between single sonications was needed to allow the abdominal wall temperature to decrease after sonication, as well as to re-oxygenate the animal between each breath-hold.

Histopathology

After fixation, the liver was serially sliced to map thermal lesions. Samples were formalin-fixed and paraffin-embedded before examination by light microscopy. Analysis was performed after haematoxylin-eosin staining in a blind fashion by the pathologist in order to describe the characteristics of the thermal lesions: localisation, size, shape, degree of tissue injury. The analysis of samples from the anterior abdominal wall was also performed in cases of injury suspicion.

Size measurements of ablation zones

Thermal dose contours were given in cross-sectional images at the focus location and in one longitudinal image. Ablation size assessment from MRI was done from T1-weighed images, also including an intermediate zone when this was observed, immediately after HIFU procedure and after one week for animals included in the survival protocol. As for histopathology, two cross-sectional values were measured in addition to the ablation zone length. Cross-sectional and length differences of ablation zones between target, calculated thermal dose, post-procedural MRI, one-week control MRI and histopathology were calculated as follows for all single cell sonication procedures: target minus histopathology, thermal dose minus histopathology, and post-procedural MRI minus one-week control MRI. Non-parametric statistical data analysis was used.

Post-procedural animal care and control

Intermittent intramuscular Buphrenorphine was administrated as analgesia during the first three postoperative days and the animals were allowed free access to food and water. Body temperature and blood samples were collected on a daily basis during that period. Blood samples were analysed for general (haemoglobin, white blood cells with differentiation, C-reactive protein, creatinine), liver-specific (bilirubin, alaninaminotransferasa, aspartatamaminotransferasa, gammaglutamintransferasa, international normalised ratio) and immunologic (interleukin, interleukin 1b, interleukin 6, interleukin 8, tumour necrosis factor) tests.

7.4 Statistics

Statistical analyses were carried out using SPSS software. The main data are given as median (range or 95% confidential interval) or number (percentage) and presented in accordance with the intent-to-treat concept. The Kaplan-Meier method and the life tables were applied for survival analyses. For the analysis of continuous variables, the Mann-Whitney *U* test was used. For comparison of frequencies, the chi-square or the Fisher exact test was performed, as appropriate. For survival comparisons, the log-rank test was applied.

8 SUMMARIES OF PAPERS

Paper I: **Laparoscopic liver resection for malignant and benign lesions: 10 year Norwegian single centre experience**[48]

During 1998-2008, Rikshospitalet accumulated a considerable experience in laparoscopic liver surgery: 139 patients, 176 resections in 149 procedures (Figure 2, Paper 1). In 2000, we established the database which has been prospectively updated. There were 113 patients with malignant lesions, including 106 patients with metastatic tumours (96 colorectal metastases and 6 carcinoids) and 7 with primary liver tumours (5 hepatocellular carcinoma, 2 cholangiocarcinoma) (Table 1, Paper 1). There were 27 patients with benign liver lesions including 7 liver cysts, 6 haemangiomas, and 5 focal nodular hyperplasia.

Analysis of these data revealed good surgical and oncologic outcomes of laparoscopic liver resection. The rate of conversion to laparotomy was 3.4%, and the median operative time and blood loss were 164 minutes and 350 ml, respectively (Table 4, Paper 1). There were levels of 6.7% intraoperative and 12.6% postoperative complications. Postoperative mortality was 0.7% (one patient). The median postoperative stay and opoid requirement were 3 days and 1 day, respectively. Tumour-free resection margins (visualised by histopathology) were achieved in 94% malignant specimens. There were small but significant differences in operative time and blood loss between procedure for benign and malignant liver lesions.

This study showed that in current days with the application of advanced laparoscopic equipment, anatomic resections do not provide better surgical or oncologic outcomes (Table 5, Paper 1). Therefore, the concept of preference of parenchyma-sparing non-anatomic, if necessary multiple, liver resections has received strong support.

This paper has also emphasised the importance of proper teaching, issues of the generation gap in surgery and the impact of healthcare management on all levels in the promotion of the development and the wider application of this patient-friendly treatment around the world.[122-124]

We concluded that, in experienced hands, laparoscopic liver resection is a favourable alternative to open resection. Perioperative morbidity and mortality, and survival following the laparoscopic resection of colorectal metastases, seem comparable to that of open resections.

Apropos, we would like to cite the words of Prof. Michel Gagner, a recognised pioneer of advanced laparoscopy and laparoscopic liver surgery, published in the *Archives of Surgery* as a commentary to this manuscript: “The myth of increased venous gas emboli from laparoscopy is shattered.”[125]

Paper II: **Laparoscopic resection of colorectal liver metastases: Surgical and long-term oncologic outcome**[117]

One hundred patients undergoing surgery in 118 procedures between August 1998 and June 2009 at Rikshospitalet were included. Survival predicted by Fong’s and Basingstoke Predictive Index (BPI) scores were taken as reference values for observed survival.[126,127]

The patients had median Fong’s and BPI’s scores of 2 (0-5) and 7 (0-23), respectively (Table 1, Paper 2). Mainstream analysis of hospital data was done on an intent-to-treat basis. Intraoperative incidents and postoperative complications were analysed according to the Satava and Clavien-Dindo classifications, with their adoption enabling application to laparoscopic liver surgery. Median follow up was 24 (0-100) months.

One hundred and seventeen non-anatomic and 34 anatomic liver resections were performed (Table 4, Paper 2). The median operative time and blood loss was 192 min and 300 ml, respectively (Table 5, Paper 2). Intraoperative incidents occurred in 14 cases (11.9%) including 5 (4.2%), 8 (6.8%) and 1 (0.8%) cases of grade I, II and III, respectively (Table 6, Paper 2). Postoperative complications were observed in 16 cases (14.3%) including 2, 3, 7, 3, 0 and 1 cases of Grade I, II, IIIa, IIIb, IV and V, respectively (Table 7, Paper 2).

At follow-up, 32 (29.9%) patients were dead, 19 (16.2%) were alive with uncured disease recurrence, and 56 (52.3%) patients were alive and disease-free. The latter group of patients included 14 (13.1%) patients who were cured for metastatic recurrence.

Hepatic recurrence occurred in 45 (42.1%) patients after a median of 7.5 (2-47) months. During follow-up, 21 repeated liver resections were performed, including 12 by laparoscopy and 9 by laparotomy (Figure 1, Paper 2). Additionally, radiofrequency and cryoablations were performed in 9 and 1 cases, respectively. Pulmonary metastases developed in 29 (27.1%)

patients in median of 9 (2-56) months after the procedure and 14 lung resections of colorectal metastases were performed, including 2 cases via thoracoscopy. No port site-metastases were registered. Local recurrence of primary colorectal cancer was registered and resected in 3 (2.8%) patients.

The 5 year overall survivals were 51% as laparoscopically-completed cases and 47% as intent-to-treat (Figure 2, Paper 2). The observed actuarial survival values exceeded the values expected by Fong's and the BPI score with 10.2% and 6.7% as laparoscopically-completed cases and with 3.8% and 2.4% as intent-to-treat, respectively (Table 8, Paper 2).

In our series, the discordance between intent-to-treat and per protocol outcomes (laparoscopically-completed cases) was statistically insignificant, i.e. "the intent was reached" (Table 5, Paper 2). This indicates that one can consider the laparoscopic technique as a well-established reliable method in the surgical treatment of colorectal liver metastases.

Laparoscopic resection appeared as a favourable alternative to open resection, as it is associated with low morbidity and mortality and a beneficial postoperative course.

Oncologic outcome, including long-term survival, is comparable to or better than that of open surgery; the observed actuarial survival is better than expected by Fong's BPI scoring systems. Laparoscopic repeated resections with the parenchyma-sparing technique play an important role in this improvement.

The study has also enabled the development of the following general conclusions: 1) the development and popularisation of a universal classification system of surgical complications amenable to both open and laparoscopic surgery is an urgent issue; 2) reporting of both intent-to-treat and per protocol outcomes should become a routine principle applied in the research of new surgical modalities, as this principle gives a comprehensive outcome picture for a reader, reduces bias in outcome presentation and enables the reliability of new surgical techniques to be measured; and 3) a new distinguished definition of disease-free and recurrence-free survival is warranted and should receive wide acceptance in the surgical society, as this definition more precisely corresponds to the current development of surgical oncology.

Paper III: **Is Laparoscopic Repeat Hepatectomy Feasible? A Tri-institutional Analysis**[128]

Laparoscopic liver resection has become a viable alternative to open hepatectomy. Multiple centres throughout the world have reported laparoscopic-assisted or totally laparoscopic liver resections including major hepatectomies.[129] With increasing data showing improved survival following repeat hepatic resection for recurrent colorectal liver metastases, demand for repeat hepatic resections is increasing.[78,130,131]

Despite recent advances in operative technology and the field of liver surgery, repeat hepatic resections are traditionally performed in an open fashion. Complexity of liver anatomy and challenges of repeat operation have prohibited the adoption of laparoscopic techniques for repeat hepatic resections among hepatobiliary surgeons. Our institution collaborated with two other pioneer centres in laparoscopic liver surgery, one French centre (group of Prof. Brice Gayet) and one American (group of Prof. Joseph Buell).

We intended to evaluate safety, feasibility, oncological integrity, and outcomes of laparoscopic repeated liver resections, and to outline the selection criteria for this approach.

An intent-to-treat analysis was performed. From 1997 to 2009, 76 laparoscopic repeated liver resections have been attempted. Operative indications were metastasis (63), hepatocellular carcinoma (3), and benign tumours (10). All patients had one or more prior liver resections (28 open, 44 laparoscopic), including 16 major resections (en-bloc removal of 3 or more Couinidad segments) (Table 2, Paper 3).

Eight cases were converted (11%) to open resections (7) or radiofrequency ablation (1) due to technical difficulties or haemorrhage. Laparoscopic repeated liver resections included 49 wedge or segmental and 19 major hepatectomies (Table 4, Paper 3). Median blood loss and operative time were 300 ml and 180 min (Table 3, Paper 3). Patients with prior open liver resection experienced more intraoperative blood loss and transfusion requirements than those with prior laparoscopic resections (p= 0.02, p= 0.01). R_0 resection was achieved in 58 (92%) patients with malignant tumours. The incidence of postoperative complications and duration of hospital stay were not statistically different between patients primarily operated upon via either laparoscopy or laparotomy. Major complications occurred in 6 (8%) cases (Table 6, Paper 3). There were no perioperative deaths. Median tumour size and number was 25 (5-125) mm and 2 (1-7), respectively. Median follow-up was 23.5 (0-86) months. There was no port-site metastasis. The 3-year and 5-year actuarial survival for patients with colorectal metastases were 83% and 55%, respectively (Figure 3, Paper 3).

We concluded that laparoscopic repeat liver resection was feasible, safe, and oncologically adequate. The short-term results were comparable with laparoscopic primary liver resections, and are superior to repeat liver resections performed in an open fashion. In patients with colorectal metastasis, intermediate and long-term oncologic results appear to be similar to the best series reported for open counterparts. Due to less operative blood loss and a lower requirement for blood transfusions, the best candidates for laparoscopic repeat resections are those with prior laparoscopic resections.

Paper IV: **Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments[82]**

Despite tremendous advancements in the field of laparoscopic hepatobiliary surgery related to both operative techniques and instrumentation, most laparoscopic liver resections still are mainly performed for easily accessible lesions.[80] Totally laparoscopic liver resection of lesions located in the posterosuperior segments is reported to be technically challenging.[132] This study aimed to define whether these technical difficulties affect the clinical outcome.

A total of 220 patients underwent laparoscopic liver resection during 244 procedures from August 1998 to December 2010. The patients who underwent primary minor single liver resection for malignant tumours affecting either posterosuperior segments 1, 7, 8, and 4a (group 1) or anterolateral segments 2, 3, 5, 6 and 4b (group 2) were included in the study (Figure 1, Paper 4). Seventy-five procedures were found to be eligible for the study, including 28 patients in group 1 and 47 patients in group 2. The majority of liver tumours in both groups were colorectal metastases. Intraoperative unfavourable incidents were graded on the basis of the Satava approach and postoperative complications were graded in agreement with the Accordion classification (Clavien-Dindo-Strasberg classification).

To reach the most problematic segments (7 and 8), four laparoscopic port sites were usually required. The patient's right abdominal side was elevated up to between 45° and 60°. Usually, 12-mm port sites were used to enable the application of a wide range of laparoscopic instruments and devices. Patient positioning and trocar placement should be carefully adjusted according to the tumour location and patient constitution (Figure 2, Paper 4).

No conversions to open surgery occurred in either of the studied groups. The operative time (median, 127 min) and blood loss (median, 200 ml) were equivalent in the two groups (Table

5, Paper 4). The rates for blood transfusions and intraoperative accidents did not differ statistically between the groups. The median tumour size was similar in the two groups. No significant difference in weight or dimensions of the resected liver specimen was observed. A tumour-free margin resection was achieved in 94.7% of the procedures, and was equivalent in both groups (Table 6, Paper 4). The postoperative course was similar in the two groups. Postoperative complications developed in 2 cases (7.1%) in group 1 and 2 cases (4.3%) in group 2 ($p = 0.626$). The median hospital stay was 2 days in both groups.

The study verified that laparoscopic liver resection for lesions located in the posterosuperior segments represents certain technical challenges. However, we have proven that the appropriate adjustment of surgical techniques and optimal patient positioning enables the laparoscopic technique to provide safe and effective parenchyma-sparing resections for lesions located in both the posterosuperior and anterolateral segments.

Paper V: Acute and survival studies of extracorporeal magnet resonance guided high intensity focused ultrasound ablation in the swine liver[133]

Among the different options for liver ablation radiofrequency, laser and cryoablation are currently the most popular methods. [134] [135] [136] However, these methods are still associated with a high risk of tumour recurrence. HIFU is a recently introduced modality for liver ablation with fast-growing popularity.[98,137,138] HIFU ablation can be performed non-invasively, the site and shape of the lesion can be chosen and lesions are precisely defined;[109] it can also potentially be performed without general anaesthesia and without any risk of tumour seeding due to needle tracks.[110,111]

An experimental study on the porcine model was designed to develop extracorporeal MR-guided HIFU ablation of the liver for its further application in patients.

Thirteen Norwegian land swine were used for the development of extracorporeal HIFU ablation of the liver in the porcine model monitored by MRI. The thermal ablation experiments were performed with a Sonalleve MR-HIFU platform (Philips Healthcare, Vantaa, Finland), integrated to the bed of a 3T MR scanner (Achieva, Philips).

Seven animals were used for the development of ablation protocol in the non-survival acute experiment and the remaining 6 animals for the optimisation of the ablation protocol in the survival experiment.

All swine were anaesthetised with Pentobarbital, Isofluran and Morphine.[120] Tracheotomy was applied for the acute series, whereas survival pigs were intubated. A Hickmann catheter was placed in the vena jugularis externa in the survival series in order to draw blood samples in the postprocedural period. The skin in the actual region was carefully shaved to facilitate the propagation of ultrasound waves. Animals were transferred to the MR room and placed in prone position with their liver facing the HIFU transducer. Respiration was stopped in expiration for 1-2 min during the MR scanning and HIFU-sonication. Prior to the respiration pauses, the swine were hyperventilated to guarantee adequate oxygenation during respiration pauses. Animals in the acute series were immediately euthanised after MR post-procedural imaging. The whole liver and abdominal skin sample (if suspected thermal damage) were resected for histopathology analysis. Swine in the survival series were awakened and kept alive for an average of 8 days (range 7-9). After follow-up MRI examination, they were euthanised and their liver/skin samples were resected for histopathology analysis.

The anaesthetic protocol was successful in all cases; pCO2 was recovered within 2-3 minutes of hyperventilation. The median total procedure time was 380 (265-640) min (Table 1, Paper 5). There was no statistical difference between target and histology cross-section measurements (Table 2, Paper 5). This was true in regard to the ablation length as well in the absence of MR registration of heat sink. When heat sink was observed, ablation length appeared to be reduced compared with the target value.

Thermal dose calculation shows no or little differences compared to histopathology measurements for normal heating and heat sink respectively. There was no statistically significant difference between ablation size determined by post-procedural MRI and histopathology, both for normal heating and heat sink, respectively. There was no difference in ablation size between post-procedural MRI and one-week control MRI measurements in the survival series.

The ordinary sonication protocol, which is primarily elaborated for uterine fibroid ablations (maximal acoustic power of 200 W, sonication duration up to 67.4 s), resulted in reversible alterations of the liver parenchyma (mostly bleeding) (Figure 3B, Paper 5). Application of ablations with a multi-cycle sonication protocol provided liver parenchyma ablation confirmed by radiological examination, with no gadolinium contrast uptake in the ablation zones. However, histopathology structural observations showed only partial coagulative necrosis (Figure 5, Paper 5). The application of high energy ablations (300-350 W, sonication duration 20.5 s) together with a multi-cycle protocol has provided complete coagulative necrosis liver tissue, as confirmed by structural histopathologic observation (Figure 6, Paper 5). Tissue vaporisation and cavitation occurred at this acoustic power level and the hyperthermia regime was different than at ablation created with 200W acoustic power. This regime resulted in a larger ablation volume than planned due to the observed cavitation.

Histopathology was more marked in the periphery of the ablation rather than in the centre, forming two ablation zones – central and peripheral – in this way (Figure 3, Paper 5).

Non-intended injuries were recorded in 3 out of 9 animal cases that underwent HIFU treatment. They were presented as burn injuries of the abdominal wall in swine with the multi-cycle low energy protocols (within 200 W). Potential near field heating was detected using MR thermometry in all of these cases. These unintended injuries were associated with long cumulative sonication time.

We concluded that extracorporeal HIFU ablation of the liver under 3 Tesla MR guidance is feasible but challenging due to the high vascularity of liver parenchyma. However, the optimal acoustic power for successful ablation remains to be determined. The impact of multi-cycle protocol, issues of functional analysis of irreversible tissue damage and power-dependant threshold to cavitation onset require further studies in order to enable the safe application of this technique for liver ablation in a clinical setting.

9. DISCUSSION

9.1 Laparoscopic liver resection for benign and malignant liver lesions

Laparoscopic liver resection was associated with low morbidity in our series. Intraoperative incidents and postoperative complications developed in 6.7% and 12.6%, respectively. 30-day mortality was comparable to that of open surgery (below 1%).

Bleeding and biliary leakage are related to surgical experience and skills, although the availability of high-tech surgical equipment has reduced these problems.[139] In addition, tumour location and size are associated with complication hazards. The low rate of postoperative infections observed with the laparoscopic technique may be an important gain in prevention of post-resection liver failure.[140]

Quite similar surgical results of liver resection for benign and malignant liver lesions were demonstrated in our series, although the latter group of patients had worse physical statuses and a higher rate of previous laparotomy and liver resection (Table 4, Paper 1).

Laparoscopic liver surgery was introduced in 1992, but this technique has not yet been generally accepted.[27,39,42,43,45,46,49-53,141-144] The development of surgery has been faster than the evolution of the hospital and university administration.[87] Most hepatobiliary centres perform barely-open hepatectomies. Open procedures still dominate, even in the majority of centres performing laparoscopic hepatectomies. Technical aspects of liver resection are still a matter of debate, even if the major challenges have been resolved and accepted; it remains time-consuming and difficult to attain mastery in laparoscopic hepatectomy. Many "traditional" surgeons promptly learned simple laparoscopic procedures, but find it rather demanding to learn more technically advanced procedures. Owing to the high specialisation within the units performing liver surgery, simple cases for laparoscopic training are not easily available. This is the main reason for the lack of fundamental laparoscopic skills among the senior generation of consultant surgeons in specialised hepatobiliary centres, which again holds back the rapid development of laparoscopic liver surgery in general as well as in individual centres.

The concept of segment-orientated anatomic hepatectomy has made an important contribution to the recent development of liver surgery.[145] Anatomic resections have been demonstrated to be associated with better haemostasis and the control of bile leakage as compared to non-anatomic resections.[146] On the other hand, new surgical technologies of ultrasound and coagulation-based parenchyma transection have reduced the benefits of anatomic resection.[147] A fairly increased operative time for anatomic resections was the only difference observed between anatomic and non-anatomic techniques in our series (Table 5, Paper 1).

Formal hemihepatectomies represent special concerns and are coupled with significantly increased technical challenges. Subsequently, this leads to a more time-consuming operation. In the early period, we mainly carried out minor resections, but, after having accumulated experience, we started to accept all groups of patients considered in conformity with classical rules of open liver surgery. Despite the intraoperative technical challenges of major resections, the laparoscopic method still results in an improved postoperative course, as also shown by others.[46] A recent multicentre study including 210 patients reported good clinical outcomes of laparoscopic hemihepatectomies with a mortality below 1%.[148]

Good skills in advanced laparoscopic surgery and liver surgery are essential. Surgical transection equipment could be improved. Prospective bilateral interactions between surgeons and industrial engineers is therefore of high importance.[149]

In spite of the routine use of 12 mm trocars, we did not place sutures on the fascia in case of the application of the radially-dilating trocar system. Nonetheless, we did not examine any cases of trocar hernia in our series; therefore, we can state that with the radially-expanding troacar system, there is no need to routinely suture the fascial layer if trocars up to 12 mm are utilised.

Learning is a crucial point of liver resection.[150] The availability of several high-resolution large size monitors in the operating room allows surgeons to examine not only intraoperative ultrasonography but also preoperative imaging, including three-dimensional reconstruction of vessels and bile ducts. This may further facilitate intraoperative navigation and contribute to learning by enabling interactive intraoperative discussion between experts and fellow surgeons to adjust surgical tactics based on the analysis of pre- and intraoperative imaging and current procedural circumstances.[151-153]

One cannot anticipate the prompt and uncomplicated introduction of laparoscopic liver surgery without the support of healthcare management.[154] Fellow surgeons should be encouraged to attend expert centres to learn “how to do it”. Experts have an ethical duty to share their knowledge with local and guest fellow surgeons and to visit other centres to perform demonstrative pilot cases. Educational training programs organised by professional societies should also be encouraged. Nevertheless, without a collaborative atmosphere in departments of hepatobiliary surgery and the individual surgeon's fervour it would be difficult to thrive in this complicated field of surgery.

9.2 Laparoscopic liver resection for colorectal liver metastases

Our studies demonstrated that laparoscopic liver resection could be safely applied in regard to colorectal metastases in the liver by an experienced team. The operation has low morbidity and postoperative mortality and good short- and long-term oncologic results.

It has been reasoned that intent-to-treat analysis is advantageous over per protocol analysis.[155] Besides, a discordance between intent-to-treat and per protocol analysis may play a role as a reliable measuring tool of a well established new treatment modality.[156] In our series, the discordance between intent-to-treat and per protocol outcomes (laparoscopically-completed cases) was very small and statistically insignificant, i.e. "the intent was accomplished". This suggests that the laparoscopic technique can be deemed as a well-established reliable method in the surgical treatment of colorectal metastases in the liver. Reporting of both intent-to-treat and per protocol outcome computations are presently uncommon in surgical science; however, this principle gives a comprehensive outcome picture for a reader, decreases a bias in outcome presentation and allows the reliability of a new surgical method to be measured. Thus, we advocate this principle to be routinely applied in the research of new surgical techniques in regard to both prospective and retrospective studies.

Patient selection for surgery is challenging, but it is a prerequisite of good treatment results. In an attempt to systematise the patient selection, several scoring methods have been elaborated. However, they have limited clinical value for patients with metastatic colorectal cancer.[157] Over the last decades, improvement in surgical and oncological outcome following resection of colorectal liver metastases has been observed. This progress has endorsed the implementation of wider indications for hepatectomy. A multimodal approach implying repeated liver resections, ablative modalities and chemotherapeutic down-staging has allowed the treatment of patients who were not previously candidates for surgery.[158]

Fine needle aspiration biopsy of liver lesions has been reported to cause tumour dissemination and adversely affect survival; also, perfection in preoperative tumour staging due to advanced imaging and interventional techniques has made needle biopsy of liver lesions futile.[159] Consequently, in our series, preoperative biopsy was used in a few cases only and mainly in an earlier period. Laparoscopic exploration is a preferable initiation of surgical intervention.[160] If there is preoperatively unrecognised inoperability, the surgeon can avoid unnecessary laparotomy, and in the case of a resectable tumour, the surgical team can choose between a laparoscopic or open approach.

Increased operative time and a tendency to a higher rate of intraoperative unfavourable incidents were registered in patients undergoing long-lasting neoadjuvant chemotherapy, as reported by others.[161] However, this has not worsened the postoperative course and rate of postoperative complications.

The postoperative course was equal whether the intent-to-treat or per protocol analysis was applied: the median duration of postoperative stay was just 3 days (2 days in present); the vast majority of patients started to consume fluids on the day of operation and almost all patients started to consume solid food on the first postoperative day.

The five year overall actuarial survival after laparoscopic liver resection was 51% in laparoscopically-completed cases and 47% in intent-to-treat in the series of colorectal liver metastases. These values correspond to the best reported outcomes after open liver resection and are better than outcomes from our own earlier reported experience with open surgery (29%).[162-164] The possible contribution of laparoscopic techniques to this improvement may be explained by a decreased impairment of the immune system due to less traumatic intervention[165,166]; nevertheless, this hypothesis should be further studied. However, the results of open surgery have improved during the last decade as well,[167] therefore our outcomes after open liver resection need to be re-evaluated.

Laparoscopic approach facilitates repeated parenchyma-sparing resections due to minimal adhesion formation and the operation is also better tolerated by patients. Parenchyma-sparing liver resection should thus be carried out whenever possible.[28] Some studies advocated that anatomic resections could potentially provide better oncological outcomes,[168,169] but this hypothesis has been shown to be unclear.[170,171] Our series designate equal survival and liver recurrence rate after anatomic and non-anatomic liver resections of colorectal metastases. The parenchyma-sparing concept increases the possibilities for repeated resections and the probability to maintain sufficient liver functional reserve thereafter.[172,173] In this context, it could extend patient life.

Our patients had quite advanced disease. About half of our patients had synchronous metastases and more than two third had primary tumour Dukes stages C and D. Both the Fong score and the BPI score have been applied for patient evaluation. The BPI score looked to be more precise with regard to survival prediction. We have recorded a better observed actuarial survival than could be expected from the Fong and the BPI scores (2.6-10% and 0.3-6.7%, respectively) (Table 8, Paper 2). One can attribute this improved survival to the contribution of the laparoscopic technique; however, such a hypothesis should be further studied in prospective randomised studies. Both the Fong and the BPI scoring systems have been developed based on the analysis of patients operated upon via the open approach.

Tumour recurrences happened in the liver in 45 patients and in the lungs in 29 patients (Figure 1, Paper 2). No port-site metastases were registered, which could be attributed to a meticulous maintenance of developed routines to minimise the risk of port-side metastases.[174] Many of the hepatic and pulmonary recurrences were treated by surgical radically-considered resections. This resulted in the fact that, despite a low five-year recurrence-free survival rate of 24%, the five-year disease-free survival was 42%, approaching the five-year overall survival of 51% (Figure 2, Paper 2).

It may even be reasonable to attempt resection of extrahepatic disease in selected patients. It is crucial to note in this regard that the classical definition of cancer-related survival after surgery does not distinguish between recurrence-free survival and disease-free survival (disease-free survival typically corresponds to recurrence-free survival in our definition). The concept of distinguishing between recurrence-free and disease-free survival is not new and it was earlier accidentally used in surgical oncology.[175] However, multiple and repeated interventions and parenchyma-sparing techniques in patients with metastatic colorectal disease have been discussed and performed over the last decade. It is thus necessary to distinguish between the terms ”recurrence-free” and ”disease-free survival” in order to justify the new approach and to obtain more precise documentation of oncologic results.

Hepatectomy for colorectal metastases has changed from a single surgical attempt to a multi-modal treatment approach of recurrent metastatic disease including surgery, local ablation, chemotherapy and parenchyma-increasing techniques such as portal vein embolisation. Therefore, multimodal treatment has transformed the disease from a rapidly deadly disease to a more chronic condition.

9.3 Laparoscopic repeat liver resections

Repeat hepatectomies have been reported by several centres, but they are actually performed infrequently. The usual indication for recurrent hepatic resection is local recurrence of colorectal liver metastasis.[12-15.] Repeat hepatectomy is quite a challenging procedure.

A key point of this study was the extensive experience of all participating institutions in laparoscopic liver surgery (our centre; Department of Digestive Diseases, Institut Mutualiste Montsouris – the group of Prof. Brice Gayet, Paris, France; Departments of Surgery, University of Louisville, the group of Prof. Joseph Buell, Louisville, USA). The rate of postoperative complication (32%) and bile leakage rate in particular following repeat laparoscopic liver resection (6.6%) corresponds to the rate previously reported for laparoscopic primary liver resections (Table 7, Paper 3).[5,7,9,10,22] Zero mortality and an acceptable conversion rate (11%) underlines the laparoscopic technique as a viable option to the open counterpart for the management of recurrent disease (Table 8, Paper 3). Intraoperative haemorrhage and transfusion requirements in this series were quite similar to those reported for primary laparoscopic hepatectomies. When comparing the group of prior laparoscopic liver resection with the group of prior open liver resection, reoperation after a previous laparoscopic procedure was associated with a lower bleeding and transfusion requirement (Table 3, Paper 3). These data may be construed by increased adhesions after an open liver resection, requiring wide adhesiolysis. After loosening of abdominal adhesions with the identification of normal anatomical landmarks, both groups underwent identical operations with similar postoperative course.

Although laparoscopic repeat liver resection following open hepatectomy is associated with higher blood loss and transfusion requirements, the surgical outcomes are acceptable when compared to laparoscopic primary liver resection series (Table 6, Paper 3).

Multiple series of open repeat liver resections for colorectal metastasis showed higher intra-operative haemorrhage with longer durations of hospital stay for open repeat liver resection versus the laparoscopic repeat liver resection group (Table 8, Paper 3). This observation persisted even in the subgroup analysis of patients with prior open liver resection undergoing laparoscopic repeat liver resection.

The laparoscopic technique is preferable for repeat liver resections in our group, regardless of the approach for primary liver resection. The criteria for the application of laparoscopic approaches for laparoscopic repeat liver resection were the same as for laparoscopic primary liver resection. The necessity of biliary or vascular reconstruction was deemed the only ultimate contra-indication to laparoscopic repeat liver resection. The surgeon performing laparoscopic repeat liver resection should have sufficient experience and should have mastered the corresponding primary laparoscopic liver resection.

Intraoperative ultrasound presents a crucial tool to perform repeat hepatectomy as the number of lesions found intraoperatively was underestimated in 12%, and overestimated in 8% of the cases in our series. Scrupulous ultrasound examination resulted in a high rate of R_0 liver resections (92%). One area of concern in this and other series has been a diminished resection margin. In the present series, the pathologic margin was less than 1 mm in 8%. Apparently, laparoscopic liver resection often utilises various methods of surgical technology, including staples. These technical tools may artificially lessen the surgical margin, as anatomical fixation does. In spite of this confusing fact, our results are parallel to those reported for laparoscopic primary liver resection and open repeat liver resection. In our experience, the location of the tumour in proximity to important vascular structures and the potential size of the liver remnants are critical factors in dictating the magnitude of resection margins.

Our series presents the first large series of laparoscopic repeat hepatic resections reported in the literature with equivalent safety, efficacy and oncologic integrity to other reported open resection series and primary laparoscopic resection series.

9.4 Laparoscopic liver resection for lesions located in laparoscopically difficult accessible and challenging segments

This thesis demonstrated that laparoscopic liver resection can be performed safely for lesions located in both the anterolateral and posterosuperior segments by an experienced surgical team. The low rate of perioperative adverse events (5.3% of both intraoperative unfavourable accidents and postoperative complications) and zero conversion and mortality were observed in the analysed groups.

However, operations for lesions located in posterosuperior segments (so-called “difficult segments”) are mostly reserved for open surgery, even in centres widely performing laparoscopic hepatectomy.

For tumours located in segment VII or segment VIII, non-anatomic liver resection or right posterior sectionectomy are preferable to right hemihepatectomy, as this preserves the liver parenchyma. However, these procedures are technically more challenging. Although only a small volume of liver parenchyma is usually removed in non-anatomic liver resection, these resections in segments VII-VIII are technically difficult, because the exposure of deeply located lesions is intricate and the transection plane can be rounded or angled.[53,176,177] Hanging techniques, implying mobilisation of the right liver lobe and dissection along the caval vein and up between the orifice of the right and the middle hepatic veins, enabling to hang on the right liver lobe, could be of major help.

In our series, the laparoscopic approach to posterosuperior segments was not related to major difficulties or increased morbidity; this observation has been supported by equal both intraoperative and postoperative outcomes of resections of the anterolateral and posterosuperior liver segments. Proper adjustment of trocar placement, the use of a flexible laparoscope, wide mobilisation of the right liver lobe and adequate use of gravity are of major help in such cases (Figure 2, Paper 4). We found that the availability of several high-resolution large size monitors in the operating room, enabling surgeons to view not only intraoperative ultrasound pictures but also preoperative imaging, including three-dimensional reconstruction of crucial vascular and biliary structures, was of great help (Figure 3, Paper 4). This further improves intraoperative navigation and may therefore play an important role in laparoscopic liver surgery, particularly in the case of tumours located in posterosuperior segments.[152,178]

The minimal distance from the resection line to tumour tissue was the only parameter which differed significantly between the studied groups (Table 5, 6, Paper 4). In regard to malignant liver lesions, we always aimed to attain resection with sufficiently safe resection margins, irrespective of the tumour location. The observed phenomenon might occur because of poorer exposure of the operative field during the approach to tumours located in posterosuperior segments; this resulted to increased concerns with regard to possible vascular or biliary injury. Consequently, the surgeon was able to cut closer to the tumour margin to prevent any additional risk while retaining a secure free margin. In our series, this phenomenon did not lead to a higher rate of tumour-involved resection margins, to a higher recurrence rate in the liver or to a poorer survival in the group of patients with resections of lesions located in posterosuperior segments.

Thoracoscopic access was suggested to approach segments VII and VIII.[179] This access is associated with longer operative time and opening of thoracic cavity, and may therefore result in increased complication hazards.[180,181] This indicates that the employment of thoracoscopic access is not flawless. A recent publication from Japan stated that the authors had switched from a thoracoscopic to laparoscopic approach for the resection of lesions in segment VII due to a lack of noticeable advantages.[182]

A completely laparoscopic approach was used in our series rather than the hand-assisted approach utilised by many others.[183,184] Our group believes that the hand-assisted method or hybrid techniques have a limited role.[176] These techniques supply a tactile sensation lacking during laparoscopy; however, this approach requires a larger incision, which reduces the benefits of minimally invasive surgery. Besides, fatigue in the inserted hand and air leakage represent the drawbacks of the hand-assisted method.[185] In addition, these techniques go against the educational doctrine of bilateral development of operative skills of resident surgeons; thus, these methods are considered to be lame regarding the educational perspective for the development of young surgeons. However, a hand-port could be applied in very challenging situations and tumour localisations when the surgeon does not achieve significant progress in the procedure or feels himself not fully confident without tactile control of the resection.

Intraoperative ultrasound could partially substitute the absent tactile sensation during the totally laparoscopic approach; thus, its employment during laparoscopic hepatectomy is mandatory to ensure adequate tumour identification and margin control.[186,187]

Adequate haemostatic control has been observed in both patient groups owing to the use of modern surgical equipment.

9.5 High intensity focused ultrasound ablation of the liver

Acute experiment

Our results of early acute series have shown only bleeding in areas of ablation by structural histopathology (Figure 3B, Paper 5). This urged us to find ways to adjust the protocol in order to achieve infallible tissue distraction. As a first step, we continued to use normal cells for treatment and not feedback cells. The feedback cells were developed to automatically stop sonication by the machine, based on the calculation of redundant energy application revealed by theoretical thermal dose reckoning.[188] Experience with liver ablations has shown that the HIFU machine stops sonication before sufficient temperature augmentation. This appears to be due to different properties of the liver and the uterine tissues (reference tissue for automatic machine adjustment of ablation characteristics), especially those related to vascularisation.

In swine 2, we applied a multiplication factor 1-1.2, which resulted in a calculated power that was in the region of 120-180 W. We concluded that this multiplication factor was not sufficient. Only 5 out of the 7 processed HIFU ablations were confirmed in swine 2 by histopathology (6 by MRI). Calculations based on multiplication factor 2 resulted in a recommended power in the region of 200-300 W.

Histopathology confirmed only minor reversible alterations in swine 2, 3 and 6. Having these quite dispiriting results and without any opportunity to increase an applied power over 200 W (the HIFU machine had a program limitation for the applied power for patient security), we considered multi-cycle ablation as a way to increase the alterations in the liver parenchyma (swine 7). Nevertheless the alterations after introduction of the multi-cycle protocol were still not sufficient enough to cause necrotic changes (in accordance with structural histopathology) in acute experiments.

Survival study

The initiated survival series (swine 8-13) with multi-cycle ablations (3-5 cycles) have enabled moderate histopathologic alterations presented by parenchymatous bleeding and partial necrosis to be revealed. However, the rate of burn injuries to the abdominal wall substantially increased. These more pronounced histopathologic alterations could be explained by the sufficient survival interval enabling the development of registerable alterations. The increase of the number of cycles to 24 in swine 11 caused severe and extensive alterations, but did not cause complete necrosis. At the same time this almost doubled the total time of the procedure.

It became clear that with the application 200 W for ablation, even together with the multi-cycle protocol, it is impossible to achieve complete necrosis (defined by structural histopathology) of the targeted area in the liver parenchyma. In addition to the high power of 300-350 W, sonication time was also shortened to 20.5 s; this could promote both complete coagulation necrosis due to the decreased time for temperature leak from the treatment area and the prevention of burn injury in the abdominal wall. As a consequence, our experiment finally resulted in coagulated necrosis, although we only used the 5 cycle protocol (Illustration 7). Tissue vaporisation and cavitation occurred at this acoustic power level and the hyperthermia regime was different than the ablation created with 200W acoustic power. This regime resulted in larger ablation volume than planned due to the observed cavitation.

There are various methods used to verify necrotic alterations of liver parenchyma.[189] We chose to use a conventional haematoxylin-eosin staining and reticuline staining in a few cases.

Enzyme histochemistry (nicotinamide adenine dinucleotide phosphatediaphorase and succinic dehydrogenase) have recently been used to verify tissue viability[104,190]; however, the value of these methods is not well known. The structural histopathology analysis used showed conflicting results, as coagulative necrosis was visually estimated between 5 and 10% in ablated zones. This may also indicate that histological evaluation is limited for the characterisation of heat-induced biological changes.[191] Functional alterations in tissues were reported to occur earlier than structural histopathologic changes after hyperthermia.[192,193] This discrepancy may indicate the need for more advanced characterisation methods in the assessment of successful liver ablation in addition to classical visual histopathological assessment with haematoxylin-eosin staining.[194] A visual observation of ablations with sonication and an acoustic power of 200W could support the presence of this discrepancy (Illustration 8). The created lesions were stiff compared to normal liver parenchyma and they were white-coloured i.e. their appearance resembled boiled tissue. In the mentioned case, MR-based calculated thermal dose thermometry and MRI perfusion measurements indicated tissue death in ablated regions, whereas histopathology examination with haematoxylin-eosin staining does not support these findings. Further studies are required to examine the functional tissue viability following mild HIFU hyperthermia.

Illustration 7: Microscopic picture showing complete coagulation necrosis
(magnification 100, haematoxylin-eosin staining).

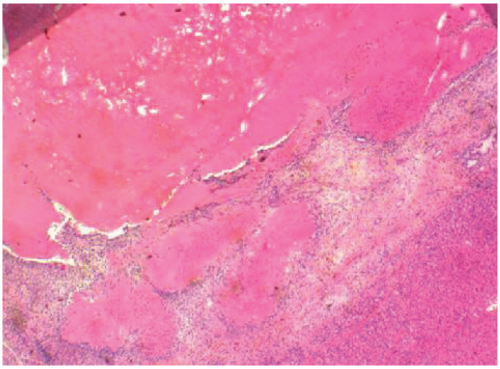
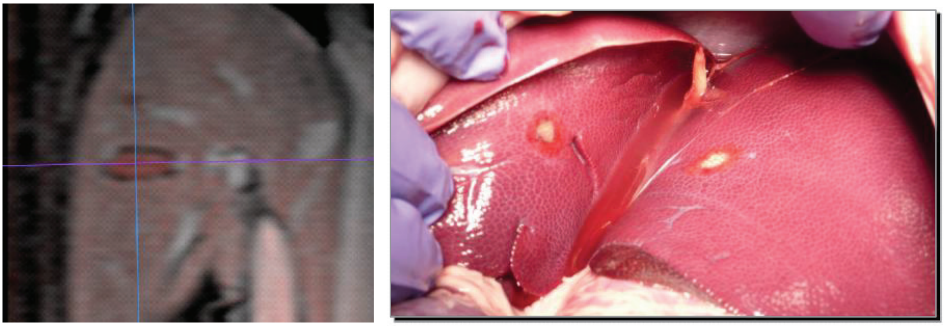


Illustration 8: Ablation lesion in the liver (swine 7): A. MR picture after liver ablation; B. Visual appearance of this lesion immediately after liver extraction.

A. **B.**



Lessons

In fact, the abdominal wall was a more probable area for non-intended thermal injury than the near field which could be concluded both from on-line temperature monitoring and from radiologic post-sonication reports, including MR-cholangiography together with histopathologic evaluation.

Although Gadolinium enhancement MRI of the liver was argued to be an excellent tool to control after ablative treatment,[195,196] our series has not shown the capacity of this technique to clearly distinguish coagulative necrosis from minor haemorrhagic alterations. Further trials to define a role of Gadolinium enhancement MRI in liver ablative therapy, and HIFU in particular, are necessary.

Due to the small volume of the performed ablations it is impossible to make definitive conclusions in regard to immunologic alteration and the release of liver enzymes into the blood. However, liver enzyme levels normalised within 3-6 days which is similar to the corresponding period for radiofrequency ablation in a clinical setting.[197] We did not observe increase in markers of immunological stress tests (interleukin, interleukin 1b, interleukin 6, interleukin 8, and tumour necrosis factor) which is promising. Nevertheless, immunologic consequences of ablative treatment required further studies.[198]

Two phenomena observed during ablation need special attention. First, the ablation also gets the intermediate zone which bounds the ablative zone from the normal non-injured liver parenchyma. In the acute series it is presented by sinusoidal congestion and in survival series by multinucleated giant cells, proliferation of fibroblasts and small bile ducts, sinusoidal congestion is minimal. The ablation zone is fully presented by a homogenous zone of coagulation necrosis in cases of high energy ablation. In cases of insufficient power, more prominent alterations develop in the periphery of the ablation zone, creating central and peripheral parts of the ablation zone (Illustration 9).

Another phenomenon was observed that needs further investigation. Small calibre vessels do not considerably influence the shape of the ablation, whereas major vessels shear ablation without any essential injury to the vessel integrity (Illustration 10). This phenomenon can be very useful in patients with tumours sitting very close to the liver hilus who are not good candidates for surgery.[199]

The application of high energy ablations (300-350 W, sonication duration 20.5 s) together with the multi-cycle protocol has provided complete coagulative necrosis liver tissue, as confirmed by structural histopathologic observation. The tissue vaporisation and cavitation that occurred at this acoustic power level and hyperthermia regime was different to that at ablation created with 200W acoustic power. This regime resulted in larger ablation volume than planned due to the observed cavitation.

Extracorporeal HIFU ablation of the liver under 3 Tesla MR guidance is feasible but challenging due to the high vascularity of liver parenchyma. Optimal acoustic power for successful ablation remains to be determined. The impact of the multi-cycle protocol, issues of functional analysis of irreversible tissue damage and power-dependent threshold to cavitation onset require further studies in order to enable the safe application of this technique in a clinical setting for liver ablation.

Illustration 9: Ablation division to central and peripheral parts. The intermediate zone bounds the ablative zone from the normal non-injured liver parenchyma.

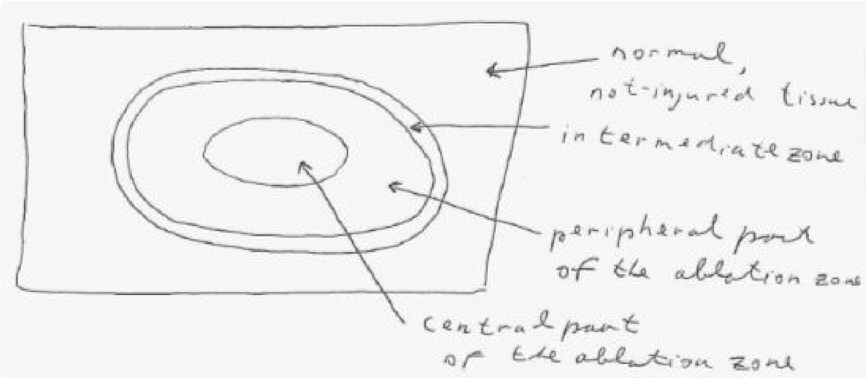
A. Schematic drawing of typical HIFU ablation in the liver parenchyma made by application of the Sonalleve MR-HIFU platform;

B. Post-procedural picture;

C. Macroscopic picture after fixation;

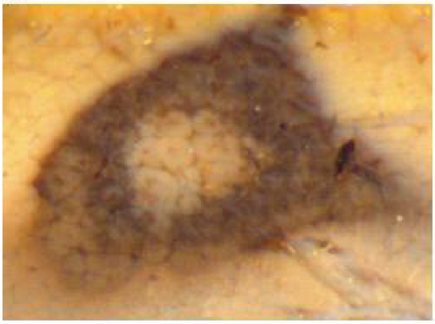
D. Microscopic picture (magnification 40, haematoxylin-eosin staining).

A.



B.

C.



D.

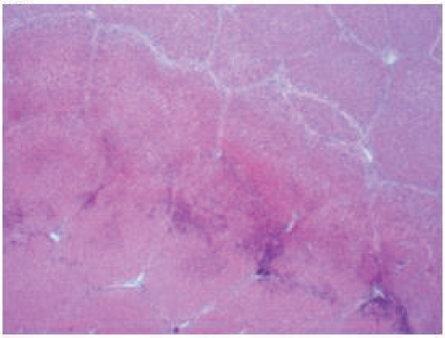
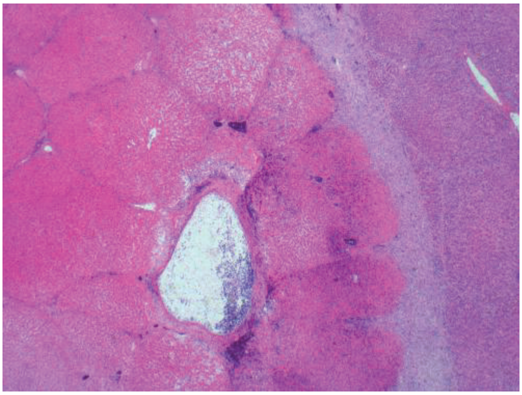


Illustration 10: A. Vessel in the peripheral parts of the ablation zone which survived ablation; B. Segmentation of the clustered ablation, which shows the irregular shape due to multiple heat sinks from surrounding blood vessels.

A:



B:

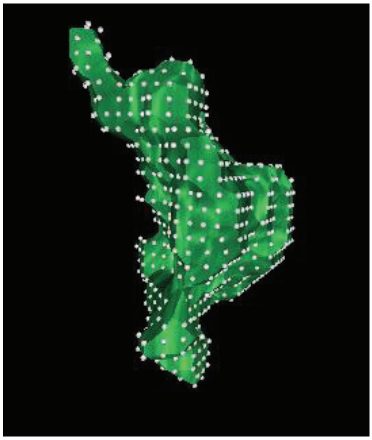


Table 3: .Overview of experimental liver ablations (Shortened and modified Tables 1 and 2 from Paper 5)

Parameters	Swine								
	Acute series				Survival series				
	2	3	6	7	8	9	10	11	13
Number of intended ablations	7	5	5	5	3	2	1	1	1
MRI and histologically-confirmed ablations (Percentage of confirmed ablations in parentheses)	5 (71%)	5 (100%)	4 (80%)	5 (100%)	3 (100%)	2 (100%)	1 (100%)	1 (100%)	(1 (100%)
Treatment cell size, mm (number of treated areas in parentheses)	8 mm (4 cases); 4 mm (3 cases)	8 mm (2 cases); 4 mm (2 cases); 12 mm (1 case)	8 mm	8 mm (4 cases); 4 mm (1 case)	8 mm	1- 8mm; 2- cluster of four treatment cells of 8 mm	Cluster of five treatment cells of 12 mm	12 mm (initial cycle) / 8 mm	2 mm (initial cycle) / 4 mm
Number of cycles	1	1	1	2 or 4	1, 5 or 7	3 or 4	3, 4 or 5	24	5
Applied power, W	80-140	120-180	200	140-200	130-200	140-200	130-200	140-200	300-350
Sonication time of single cycle, s	14.2-38.2	10.7-50.8	27.5	16-27.5	11.3-27.5	14.7-67.4	20.2-48.5	27.5-38.3	20.5
Cooling time, s*	n.a.	n.a.	167-199	64-380	43-143	34-146	78-219	116-337	533-1088
Maximal temperature, °C	67.8	81.0	90.1	89.3	82.8	≥100	≥100	82.8	≥100
Total procedure time, min Including: -Anaesthesia preparation -Planning -Sonications -Post-scanning	395 60 120 90 125	305 65 95 80 65	275 75 80 65 45	315 50 70 145 50	450 80 90 200 80	395 100 90 155 50	380 80 85 175 40	640 70 110 415 45	295 55 60 130 50
Histopathologic findings	Minor reversible, parancymatous bleeding.	Minor reversible, parancymatous bleeding.	Minor reversible, parancymatous bleeding.	Minor reversible, parancymatous bleeding.	Moderate, parancymatous bleeding, partial necrosis.	Moderate, parancymatous bleeding, partial necrosis.	Moderate, parancymatous bleeding, partial necrosis.	Severe alteration, Extensive, but not complete necrosis.	Coagulation necrosis
Gd uptake	Partial / None	Partial / None	Partial / None	Partial / None	Partial / None	None	None	None	None
Burn injury to the abdominal wall	No	No	No	No	Yes	No	Yes	Yes	No

9.6 Future aspects

What is the future of interventions in the liver?

Can laparoscopic liver surgery largely substitute its open counterpart? We may quite confidently say “yes”.

Can HIFU totally replace liver surgery? We may quite confident say “not in the near future”.

Consequently, the accumulated research, clinical and organisational experience has enabled us to initiate two new projects in this field of medical research and practice:

1. Randomised trial of laparoscopic versus open liver resection for colorectal metastases.

2. High intensity focused ultrasound ablation of the liver under 3 Tesla magnet resonance guidance: Refinement experimental study.

Study 1 will carry out evidence-based data on the following particular research issues:

A) Surgical stress and immunosuppression;

B) Economics;

C) Quality of life;

D) Long-term oncologic outcomes.

Study 2 will further develop MR-guided HIFU for liver lesions. The following points are to be studied:

1. Is coagulative necrosis defined by classical histopathologic evaluation with haematoxylin-eosin staining needed to achieve a successful HIFU liver ablation? What is the role of new markers of tissue viability (Enzyme histochemistry - nicotinamide adenine dinucleotide phosphatediaphorase and succinic dehydrogenase)?

2. What is the optimal HIFU sonication regime to obtain a successful ablation?

3. Can the HIFU properties be adjusted such as to preserve the integrity of major vessels and ensure parenchyma ablation within the ablation volume? Should major vessels be avoided in the area of planned HIFU ablation?

4. Does the non-perfused volume represent a reliable parameter for successful ablation assessment?

10. CONCLUSIONS

- Laparoscopic liver resection is a favourable alternative to open resection for both benign and malignant lesions. The rate of perioperative adverse events appears to decrease compared with open resections.
- Laparoscopic resection is a favourable alternative to open liver resection for patients with colorectal liver metastases both in regard to perioperative results and plausibly for oncologic outcome. The observed actuarial survival values after laparoscopic resection surpass the predicted survival analysed by major scoring systems in regard to open resection.
- Laparoscopic repeat hepatic resections can be performed safely and with good results, particularly in patients with prior laparoscopic resections.
- Laparoscopic liver resection for lesions located in posterosuperior segments represents certain technical challenges. However, the appropriate adjustment of surgical techniques, equipment and optimal patient positioning enables the laparoscopic technique to provide safe and effective parenchyma-sparing resections for lesions located in posterosuperior segments.
- A randomised study to finalise the observed benefits of laparoscopic technique both in relation to perioperative morbidity and oncologic outcomes is warranted.
- Extracorporeal MR-guided HIFU ablation in the liver is a challenging ablation modality due to the high vascularity of liver parenchyma.
- Further studies to develop and optimise MR-guided HIFU ablation of liver lesions. In particular, the impact of the multi-cycle sonication protocol, issues of functional analysis of irreversible tissue damage and power-dependent threshold to cavitation onset require further studies.

11. REFERENCE LIST

1. Pare A. The apologia and treatise of Ambroise Pare. Ney York: NY: Dover Publishing; 1968.

2. Foster JH. History of liver surgery. Arch Surg 1991 Mar;126(3):381-7.

3. McClusky DA, III, Skandalakis LJ, Colborn GL, Skandalakis JE. Hepatic surgery and hepatic surgical anatomy: historical partners in progress. World J Surg 1997 Mar;21(3):330-42.

4. Felekouras DC, Kaparelos E, Papalambros E. The history og liver surgery, hepatectomy and haemostasis. Hellenic Journal of Surgery 2010;82(5):280-95.

5. Glisson F. Anatomia Hepatis. London: Typ. Du-Gardianis; 1654.

6. Kekis P, Kekis B. Surgical anatomy of the liver. In: Karaliotas CC, Broelsch CE, Habib NA, editors. Liver and Biliary Tract Surgery Embryological Anatomy to 3D-Imaging and Transplant Innovations. Wien: Springer; 2006. p. 17-33.

7. Rex H. Betrage zur morphologie der saugerleber. Morphol Jahrb 1888;14:517.

8. Cantlie J. On a new arrangement of the right and left lobes of the liver. J Anat Physiol Lond 1898;32:4.

9. Lehmann K, Clavien PA. History of hepatic surgery. Surg Clin.North Am. 2010 Aug;90(4):655-64.

10. Langenbuch C. Ein fall von resection eines linnkssetingen schnurlappens der leber. Heilung Klin Wochenschr 1888;25:37.

11. Kousnetzoff M, Pensky J. Sur la resection partielle du foie. Rev Chir 1896;16:501-21.

12. Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann.Surg 1908 Oct;48(4):541-9.

13. von Haberer H. Zur frage der nicht parasitaren leberzysten. Wien Klin Wochenschr 1909;1788.

14. Wendell W. Beeitrage zur chirurgie der leber. Arch Klin Chir 1911;95:887.

15. Couinaud C. [Anatomic principles of left and right regulated hepatectomy: technics]. J Chir (Paris) 1954 Dec;70(12):933-66.

16. Couinaud C. [Studies on intrahepatic bile ducts]. J Chir (Paris) 1954 Apr;70(4):310-28.

17. Sutherland F, Harris J. Claude Couinaud: a passion for the liver. Arch.Surg 2002 Nov;137(11):1305-10.

18. Celinski SA, Gamblin TC. Hepatic resection nomenclature and techniques. Surg Clin.North Am. 2010 Aug;90(4):737-48.

19. Lortat-Jacob JL, Robert HG. [Well defined technic for right hepatectomy]. Presse Med. 1952 Apr 16;60(26):549-51.

20. Cho CS, Park J, Fong Y. Hepatic resection. In ACS Surgery: Principles and Practice. WebMD; 2007.

21. Goldsmith NA, Woodburne RT. The surgical anatomy pertaining to liver resection. Surg Gynecol Obstet. 1957 Sep;105(3):310-8.

22. Healey JE, Jr., Schroy PC, Sorensen RJ. The intrahepatic distribution of the hepatic artery in man. J Int Coll.Surg 1953 Aug;20(2):133-48.

23. HJORTSJO CH. The topography of the intrahepatic duct systems. Acta Anat (Basel) 1951;11(4):599-615.

24. Edmondson HA. Tumors of the liver and intrahepatic bile ducts. In Atlas of tumour pathology. Washington, DC: Armed Forces Institute of Pathology; 1958. p. 25.

25. Tanagho EA, McAninch JW. Laparoscopic instrumentation and basic techniques. McGraw-Hill's AccessMedicine; 2008.

26. Chiappa A, Makuuchi M, Lygidakis NJ, Zbar AP, Chong G, Bertani E, Sitzler PJ, Biffi R, Pace U, Bianchi PP, et al. The management of colorectal liver metastases: Expanding the role of hepatic resection in the age of multimodal therapy. Crit Rev.Oncol.Hematol. 2009 Oct;72(1):65-75.

27. Edwin B, Mala T, Gladhaug I, Fosse E, Mathisen Y, Bergan A, Soreide O. Liver tumors and minimally invasive surgery: a feasibility study. J.Laparoendosc.Adv.Surg.Tech.A 2001 Jun;11(3):133-9.

28. Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y, Dematteo RP, Blumgart LH, D'Angelica M. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann.Surg 2008 Jan;247(1):109-17.

29. Evans J. Ablative and catheter-delivered therapies for colorectal liver metastases (CRLM). Eur.J Surg Oncol. 2007 Dec;33 Suppl 2:S64-S75.

30. Hebbar M, Pruvot FR, Romano O, Triboulet JP, de GA. Integration of neoadjuvant and adjuvant chemotherapy in patients with resectable liver metastases from colorectal cancer. Cancer Treat.Rev. 2009 Dec;35(8):668-75.

31. Memon K, Lewandowski RJ, Kulik L, Riaz A, Mulcahy MF, Salem R. Radioembolization for primary and metastatic liver cancer. Semin.Radiat.Oncol. 2011 Oct;21(4):294-302.

32. Mala T, Bergan A, Edwin B, Gladhaug I, Mathisen O. [Liver resection--indications and results]. Tidsskr.Nor Laegeforen. 2001 Sep 10;121(21):2476-80.

33. Adam R, McMaster P, O'Grady JG, Castaing D, Klempnauer JL, Jamieson N, Neuhaus P, Lerut J, Salizzoni M, Pollard S, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl. 2003 Dec;9(12):1231-43.

34. Semm K. Endoscopic appendectomy. Endoscopy 1983 Mar;15(2):59-64.

35. Mouret P. From the first laparoscopic cholecystectomy. Dig Surg 1987;8(3):124-5.

36. Mühe E. Die erste cholecystektomie durch das laparoskop. Arch Klin Chir 2010;369:804.

37. Reich H, McGlynn F, DeCaprio J, Budin R. Laparoscopic excision of benign liver lesions. Obstet.Gynecol. 1991 Nov;78(5 Pt 2):956-8.

38. Gagner M, Rheault M, Dubuc J. Laparoscopic partial hepatectomy for liver tumor. Surg Endosc 1992;6:99.

39. Azagra JS, Goergen M, Gilbart E, Jacobs D. Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. Surg.Endosc. 1996 Jul;10(7):758-61.

40. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, Brock G, McMasters KM. Experience with more than 500 minimally invasive hepatic procedures. Ann.Surg. 2008 Sep;248(3):475-86.

41. Cai XJ, Yang J, Yu H, Liang X, Wang YF, Zhu ZY, Peng SY. Clinical study of laparoscopic versus open hepatectomy for malignant liver tumors. Surg.Endosc. 2008 Feb 23.

42. Chen HY, Juan CC, Ker CG. Laparoscopic liver surgery for patients with hepatocellular carcinoma. Ann.Surg.Oncol. 2008 Mar;15(3):800-6.

43. Cherqui D, Husson E, Hammoud R, Malassagne B, Stephan F, Bensaid S, Rotman N, Fagniez PL. Laparoscopic liver resections: a feasibility study in 30 patients. Ann.Surg. 2000 Dec;232(6):753-62.

44. Dagher I, O'Rourke N, Geller DA, Cherqui D, Belli G, Gamblin TC, Lainas P, Laurent A, Nguyen KT, Marvin MR, et al. Laparoscopic major hepatectomy: an evolution in standard of care. Ann.Surg 2009 Nov;250(5):856-60.

45. Gagner M, Rogula T, Selzer D. Laparoscopic liver resection: benefits and controversies. Surg.Clin.North Am. 2004 Apr;84(2):451-62.

46. Gayet B, Cavaliere D, Vibert E, Perniceni T, Levard H, Denet C, Christidis C, Blain A, Mal F. Totally laparoscopic right hepatectomy. Am.J.Surg. 2007 Nov;194(5):685-9.

47. Ito K, Ito H, Are C, Allen PJ, Fong Y, Dematteo RP, Jarnagin WR, D'Angelica MI. Laparoscopic versus open liver resection: a matched-pair case control study. J Gastrointest.Surg 2009 Dec;13(12):2276-83.

48. Kazaryan AM, Pavlik M, I, Rosseland AR, Rosok BI, Mala T, Villanger O, Mathisen O, Giercksky KE, Edwin B. Laparoscopic liver resection for malignant and benign lesions: ten-year Norwegian single-center experience. Arch Surg 2010 Jan;145(1):34-40.

49. Koffron AJ, Auffenberg G, Kung R, Abecassis M. Evaluation of 300 minimally invasive liver resections at a single institution: less is more. Ann.Surg. 2007 Sep;246(3):385-92.

50. Lee KF, Cheung YS, Chong CN, Tsang YY, Ng WW, Ling E, Wong J, Lai PB. Laparoscopic versus open hepatectomy for liver tumours: a case control study. Hong.Kong.Med.J. 2007 Dec;13(6):442-8.

51. Mala T, Edwin B, Rosseland AR, Gladhaug I, Fosse E, Mathisen O. Laparoscopic liver resection: experience of 53 procedures at a single center. J.Hepatobiliary.Pancreat.Surg. 2005;12(4):298-303.

52. Rau HG, Meyer G, Cohnert TU, Schardey HM, Jauch K, Schildberg FW. Laparoscopic liver resection with the water-jet dissector. Surg.Endosc. 1995 Sep;9(9):1009-12.

53. Vibert E, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B. Laparoscopic liver resection. Br.J.Surg. 2006 Jan;93(1):67-72.

54. Marvin MR, Buell JF. Laparoscopic liver surgery. Adv.Surg 2009;43:159-73.

55. Ravindra KV, Buell JF. Laparoscopic liver surgery: a synopsis. Minerva Chir 2009 Aug;64(4):327-32.

56. Lai EC, Tang CN, Yang GP, Li MK. Multimodality laparoscopic liver resection for hepatic malignancy--from conventional total laparoscopic approach to robot-assisted laparoscopic approach. Int.J Surg 2011;9(4):324-8.

57. Casciola L, Patriti A, Ceccarelli G, Bartoli A, Ceribelli C, Spaziani A. Robot-assisted parenchymal-sparing liver surgery including lesions located in the posterosuperior segments. Surg Endosc 2011 Dec;25(12):3815-24.

58. Ribes D, Peterhans M, Anderegg S, Wallach D, Banz V, Kim-Fuchs C, Candinas D, Weber S. Image guided liver surgery. Int J CARS 2012;Online first, 17 May 2012.

59. Lamata P, Lamata F, Sojar V, Makowski P, Massoptier L, Casciaro S, Ali W, Studeli T, Declerck J, Elle OJ, et al. Use of the Resection Map system as guidance during hepatectomy. Surg Endosc 2010 Sep;24(9):2327-37.

60. Mala T, Samset E, Aurdal L, Gladhaug I, Edwin B, Soreide O. Magnetic resonance imaging-estimated three-dimensional temperature distribution in liver cryolesions: a study of cryolesion characteristics assumed necessary for tumor ablation. Cryobiology 2001 Nov;43(3):268-75.

61. Tamandl D, Gruenberger B, Herberger B, Schoppmann S, Bodingbauer M, Schindl M, Puhalla H, Fleischmann E, Schima W, Jakesz R, et al. Selective resection of colorectal liver metastases. Eur.J.Surg.Oncol. 2007 Mar;33(2):174-82.

62. Fuhrman GM, Curley SA, Hohn DC, Roh MS. Improved survival after resection of colorectal liver metastases. Ann.Surg.Oncol. 1995 Nov;2(6):537-41.

63. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008 Jan;13(1):51-64.

64. Van CE, Nordlinger B, Adam R, Kohne CH, Pozzo C, Poston G, Ychou M, Rougier P. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur.J.Cancer 2006 Sep;42(14):2212-21.

65. Cipriani F, Catena M, Ratti F, Paganelli M, Ferla F, Aldrighetti L. LESS technique for liver resection: the progress of the mini-invasive approach: a single-centre experience
4. Minim.Invasive.Ther.Allied Technol. 2012 Jan;21(1):55-8.

66. Troisi R, Montalti R, Smeets P, Van HJ, Van VH, Colle I, De GS, de HB. The value of laparoscopic liver surgery for solid benign hepatic tumors. Surg.Endosc. 2008 Jan;22(1):38-44.

67. Abu HM, Di FF, Teng MJ, Godfrey DA, Primrose JN, Pearce NW. Surgical management of benign and indeterminate hepatic lesions in the era of laparoscopic liver surgery. Dig.Surg. 2011;28(3):232-6.

68. Vanounou T, Steel JL, Nguyen KT, Tsung A, Marsh JW, Geller DA, Gamblin TC. Comparing the clinical and economic impact of laparoscopic versus open liver resection. Ann.Surg.Oncol. 2010 Apr;17(4):998-1009.

69. Mirnezami R, Mirnezami AH, Chandrakumaran K, Abu HM, Pearce NW, Primrose JN, Sutcliffe RP. Short- and long-term outcomes after laparoscopic and open hepatic resection: systematic review and meta-analysis. HPB (Oxford) 2011 May;13(5):295-308.

70. Soubrane O, Cherqui D, Scatton O, Stenard F, Bernard D, Branchereau S, Martelli H, Gauthier F. Laparoscopic left lateral sectionectomy in living donors: safety and reproducibility of the technique in a single center. Ann.Surg. 2006 Nov;244(5):815-20.

71. Troisi R, Debruyne R, Rogiers X. Laparoscopic living donor hepatectomy for pediatric liver transplantation. Acta Chir Belg. 2009 Jul;109(4):559-62.

72. Mouiel J, Katkhouda N, Gugenheim J, Fabiani P. Possibilities of laparoscopic liver resection. J Hepatobiliary.Pancreat.Surg 2000;7(1):1-8.

73. Kazaryan AM, Rosok BI, Edwin B. Laparoscopic and open liver resection for colorectal metastases: different indications? HPB (Oxford) 2010 Aug;12(6):434.

74. Mala T, Edwin B, Gladhaug I, Fosse E, Soreide O, Bergan A, Mathisen O. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. Surg.Endosc. 2002 Jul;16(7):1059-63.

75. Nguyen KT, Gamblin TC, Geller DA. Laparoscopic liver resection for cancer. Future.Oncol. 2008 Oct;4(5):661-70.

76. Abu HM, Di FF, Abu SM, Pearce NW. Oncological efficiency analysis of laparoscopic liver resection for primary and metastatic cancer: a single-center UK experience. Arch.Surg. 2012 Jan;147(1):42-8.

77. de Jong MC, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J, Hubert C, Gigot JF, Schulick RD, Choti MA, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. J.Gastrointest.Surg. 2009 Dec;13(12):2141-51.

78. Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, Encke A, Blumgart L, Fong Y. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. Ann.Surg. 2002 Jun;235(6):863-71.

79. Gutt CN, Oniu T, Schemmer P, Mehrabi A, Buchler MW. Fewer adhesions induced by laparoscopic surgery? Surg Endosc 2004 Jun;18(6):898-906.

80. Vigano L, Tayar C, Laurent A, Cherqui D. Laparoscopic liver resection: a systematic review. J Hepatobiliary.Pancreat.Surg 2009;16(4):410-21.

81. Cho JY, Han HS, Yoon YS, Shin SH. Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. Surgery 2008 Jul;144(1):32-8.

82. Kazaryan AM, Rosok BI, Marangos IP, Rosseland AR, Edwin B. Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments. Surg Endosc. 2011 Dec;25(12):3881-9.

83. Tanaka K, Shimada H, Matsumoto C, Matsuo K, Takeda K, Nagano Y, Togo S. Impact of the degree of liver resection on survival for patients with multiple liver metastases from colorectal cancer. World J Surg. 2008 Sep;32(9):2057-69.

84. Edwin B, Nordin A, Kazaryan AM. Laparoscopic liver surgery: new frontiers. Scand.J Surg. 2011;100(1):54-65.

85. Fartoux L, Decaens T. Contribution of biomarkers and imaging in the management of hepatocellular carcinoma. Clin.Res.Hepatol.Gastroenterol. 2011 Jun;35 Suppl 1:S21-S30.

86. Creeden J, Junker F, Vogel-Ziebolz S, Rex D. Serum tests for colorectal cancer screening. Mol.Diagn.Ther. 2011 Jun 1;15(3):129-41.

87. Hockerstedt K. What is new in liver surgery? Scand.J Surg 2011;100(1):5-7.

88. Robertson EG, Baxter G. Tumour seeding following percutaneous needle biopsy: the real story! Clin.Radiol. 2011 Nov;66(11):1007-14.

89. Forsbring M, Vik ES, Dalhus B, Karlsen TH, Bergquist A, Schrumpf E, Bjoras M, Boberg KM, Alseth I. Catalytically impaired hMYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma. Carcinogenesis 2009 Jul;30(7):1147-54.

90. Bentrem DJ, Dematteo RP, Blumgart LH. Surgical therapy for metastatic disease to the liver. Annu.Rev.Med. 2005;56:139-56.

91. Lencioni R, Crocetti L. Radiofrequency ablation of liver cancer. Tech.Vasc.Interv.Radiol. 2007 Mar;10(1):38-46.

92. Webb H, Lubner MG, Hinshaw JL. Thermal ablation. Semin.Roentgenol. 2011 Apr;46(2):133-41.

93. Rhim H, Dodd GD, III, Chintapalli KN, Wood BJ, Dupuy DE, Hvizda JL, Sewell PE, Goldberg SN. Radiofrequency thermal ablation of abdominal tumors: lessons learned from complications. Radiographics 2004 Jan;24(1):41-52.

94. Mala T, Edwin B, Samset E, Gladhaug I, Hol PK, Fosse E, Mathisen O, Bergan A, Soreide O. Magnetic-resonance-guided percutaneous cryoablation of hepatic tumours. Eur.J Surg 2001 Aug;167(8):610-7.

95. Vogl TJ, Eichler K, Straub R, Engelmann K, Zangos S, Woitaschek D, Bottger M, Mack MG. Laser-induced thermotherapy of malignant liver tumors: general principals, equipment(s), procedure(s)--side effects, complications and results. Eur.J Ultrasound 2001 Jun;13(2):117-27.

96. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review. Arch Surg 2006 Feb;141(2):181-90.

97. Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. AJR Am.J Roentgenol. 2008 Jan;190(1):191-9.

98. Wu F. Extracorporeal high intensity focused ultrasound in the treatment of patients with solid malignancy. Minim.Invasive.Ther.Allied Technol. 2006;15(1):26-35.

99. Wood RW, Loomis L. The physical and biological effects of high frequency sound waves of great intensity. Phil Mag. 1927;4:417-36.

100. Lynn JG, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. J.Gen.Physiol 1942 Nov 20;26(2):179-93.

101. Kennedy JE, Wu F, ter Haar GR, Gleeson FV, Phillips RR, Middleton MR, Cranston D. High-intensity focused ultrasound for the treatment of liver tumours. Ultrasonics 2004 Apr;42(1-9):931-5.

102. Park MY, Jung SE, Cho SH, Piao XH, Hahn ST, Han JY, Woo IS. Preliminary experience using high intensity focused ultrasound for treating liver metastasis from colon and stomach cancer. Int.J Hyperthermia 2009 May;25(3):180-8.

103. Leslie TA, Kennedy JE, Illing RO, ter Haar GR, Wu F, Phillips RR, Friend PJ, Roberts IS, Cranston DW, Middleton MR. High-intensity focused ultrasound ablation of liver tumours: can radiological assessment predict the histological response? Br.J Radiol. 2008 Jul;81(967):564-71.

104. Parmentier H, Melodelima D, N'Djin A, Chesnais S, Chapelon JY, Rivoire M. High-intensity focused ultrasound ablation for the treatment of colorectal liver metastases during an open procedure: study on the pig. Ann.Surg. 2009 Jan;249(1):129-36.

105. Ng KK, Poon RT, Chan SC, Chok KS, Cheung TT, Tung H, Chu F, Tso WK, Yu WC, Lo CM, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Ann.Surg 2011 May;253(5):981-7.

106. Holbrook AB, Santos JM, Kaye E, Rieke V, Pauly KB. Real-time MR thermometry for monitoring HIFU ablations of the liver. Magn Reson.Med. 2010 Feb;63(2):365-73.

107. Quesson B, Laurent C, Maclair G, de Senneville BD, Mougenot C, Ries M, Carteret T, Rullier A, Moonen CT. Real-time volumetric MRI thermometry of focused ultrasound ablation in vivo: a feasibility study in pig liver and kidney. NMR Biomed. 2011 Feb;24(2):145-53.

108. Fischer K, Gedroyc W, Jolesz FA. Focused ultrasound as a local therapy for liver cancer. Cancer J. 2010 Mar;16(2):118-24.

109. Hynynen K, Freund WR, Cline HE, Chung AH, Watkins RD, Vetro JP, Jolesz FA. A clinical, noninvasive, MR imaging-monitored ultrasound surgery method. Radiographics 1996 Jan;16(1):185-95.

110. Illing RO, Kennedy JE, Wu F, ter Haar GR, Protheroe AS, Friend PJ, Gleeson FV, Cranston DW, Phillips RR, Middleton MR. The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. Br.J Cancer 2005 Oct 17;93(8):890-5.

111. Visioli AG, Rivens IH, ter Haar GR, Horwich A, Huddart RA, Moskovic E, Padhani A, Glees J. Preliminary results of a phase I dose escalation clinical trial using focused ultrasound in the treatment of localised tumours. Eur.J Ultrasound 1999 Mar;9(1):11-8.

112. Satava RM. Identification and reduction of surgical error using simulation. Minim.Invasive.Ther.Allied Technol. 2005;14(4):257-61.

113. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992 May;111(5):518-26.

114. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann.Surg. 2004 Aug;240(2):205-13.

115. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann.Surg. 2009 Aug;250(2):177-86.

116. Porembka MR, Hall BL, Hirbe M, Strasberg SM. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the american college of surgeons national surgical quality improvement program. J Am Coll Surg. 2010 Mar;210(3):286-98.

117. Kazaryan AM, Marangos IP, Rosok BI, Rosseland AR, Villanger O, Fosse E, Mathisen O, Edwin B. Laparoscopic resection of colorectal liver metastases: surgical and long-term oncologic outcome. Ann.Surg. 2010 Dec;252(6):1005-12.

118. Kazaryan AM, Røsok B, Edwin B. Morbidity assessment in surgery: Refinement proposal based on a concept of perioperative adverse events. Surg Endosc (under consideration) 2012.

119. Kim YS, Keserci B, Partanen A, Rhim H, Lim HK, Park MJ, Kohler MO. Volumetric MR-HIFU ablation of uterine fibroids: Role of treatment cell size in the improvement of energy efficiency. Eur.J Radiol. 2011 Sep 27.

120. Halvorsen PS, Fleischer LA, Espinoza A, Elle OJ, Hoff L, Skulstad H, Edvardsen T, Fosse E. Detection of myocardial ischaemia by epicardial accelerometers in the pig. Br.J.Anaesth. 2009 Jan;102(1):29-37.

121. Kohler MO, Mougenot C, Quesson B, Enholm J, Le BB, Laurent C, Moonen CT, Ehnholm GJ. Volumetric HIFU ablation under 3D guidance of rapid MRI thermometry. Med.Phys. 2009 Aug;36(8):3521-35.

122. Sachdeva AK, Russell TR. Safe introduction of new procedures and emerging technologies in surgery: education, credentialing, and privileging. Surg Clin.North Am. 2007 Aug;87(4):853-vii.

123. Bittner JG, Coverdill JE, Imam T, Deladisma AM, Edwards MA, Mellinger JD. Do increased training requirements in gastrointestinal endoscopy and advanced laparoscopy necessitate a paradigm shift? A survey of program directors in surgery. J Surg Educ. 2008 Nov;65(6):418-30.

124. Myers JA, Doolas A. How to teach an old dog new tricks and how to teach a new dog old tricks: bridging the generation gap to push the envelope of advanced laparoscopy. Surg Endosc 2006 Aug;20(8):1177-8.

125. Gagner M. Small incision, big surgeon: Laparoscopic liver resection for tumors without a doubt: Comment on "Laparoscopic Liver Resection for Malignant and Benign Lesions: Ten-Year Norwegian Single-Center Experience". Arch Surg 2010 Jan;145(1):40-1.

126. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann.Surg. 1999 Sep;230(3):309-18.

127. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann.Surg. 2008 Jan;247(1):125-35.

128. Shafaee Z, Kazaryan AM, Marvin MR, Cannon R, Buell JF, Edwin B, Gayet B. Is laparoscopic repeat hepatectomy feasible? A tri-institutional analysis. J Am Coll Surg. 2011 Feb;212(2):171-9.

129. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann.Surg 2009 Nov;250(5):825-30.

130. Fong Y, Blumgart LH, Cohen A, Fortner J, Brennan MF. Repeat hepatic resections for metastatic colorectal cancer. Ann.Surg. 1994 Nov;220(5):657-62.

131. Ishiguro S, Akasu T, Fujimoto Y, Yamamoto J, Sakamoto Y, Sano T, Shimada K, Kosuge T, Yamamoto S, Fujita S, et al. Second hepatectomy for recurrent colorectal liver metastasis: analysis of preoperative prognostic factors. Ann.Surg.Oncol. 2006 Dec;13(12):1579-87.

132. Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez PL. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg 2003 Jul;138(7):763-9.

133. Courivaud F, Kazaryan AM, Lund A, Pavlik Marangos I, Jebsen P, Fosse E, Hol PK, Edwin B. Acute and survival studies of magnet resonance guided high intensity focused ultrasound ablation in the swine liver. J Magn Reson.Imaging (under consideration) 2013.

134. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review. Arch.Surg. 2006 Feb;141(2):181-90.

135. Vogl TJ, Straub R, Eichler K, Sollner O, Mack MG. Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy--local tumor control rate and survival data. Radiology 2004 Feb;230(2):450-8.

136. Mala T. Cryoablation of liver tumours -- a review of mechanisms, techniques and clinical outcome. Minim.Invasive.Ther.Allied Technol. 2006;15(1):9-17.

137. Hynynen K. MRI-guided focused ultrasound treatments. Ultrasonics 2010 Feb;50(2):221-9.

138. Jolesz FA. MRI-guided focused ultrasound surgery. Annu.Rev.Med. 2009;60:417-30.

139. Poon RT. Current techniques of liver transection. HPB (Oxford) 2007;9(3):166-73.

140. van den Broek MA, Damink SW, Dejong CH, Lang H, Malago M, Jalan R, Saner FH. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int. 2008 Jul;28(6):767-80.

141. Buell JF, Koffron AJ, Thomas MJ, Rudich S, Abecassis M, Woodle ES. Laparoscopic liver resection. J.Am.Coll.Surg. 2005 Mar;200(3):472-80.

142. Cai XJ, Yang J, Yu H, Liang X, Wang YF, Zhu ZY, Peng SY. Clinical study of laparoscopic versus open hepatectomy for malignant liver tumors. Surg.Endosc. 2008 Feb 23.

143. Ferzli G, David A, Kiel T. Laparoscopic resection of a large hepatic tumor. Surg.Endosc. 1995 Jun;9(6):733-5.

144. Hashizume M, Takenaka K, Yanaga K, Ohta M, Kajiyama K, Shirabe K, Itasaka H, Nishizaki T, Sugimachi K. Laparoscopic hepatic resection for hepatocellular carcinoma. Surg.Endosc. 1995 Dec;9(12):1289-91.

145. Billingsley KG, Jarnagin WR, Fong Y, Blumgart LH. Segment-oriented hepatic resection in the management of malignant neoplasms of the liver. J.Am.Coll.Surg. 1998 Nov;187(5):471-81.

146. Schwartz SI. Hepatic resection. Ann.Surg. 1990 Jan;211(1):1-8.

147. Lai PB, Lee KF, Wong J, Li AK. Techniques for liver resection: a review. Surgeon. 2007 Jun;5(3):166-74.

148. Dagher I, O'Rourke N, Geller DA, Cherqui D, Belli G, Gamblin TC, Lainas P, Laurent A, Nguyen KT, Marvin MR, et al. Laparoscopic major hepatectomy: an evolution in standard of care. Ann.Surg 2009 Nov;250(5):856-60.

149. Development of laparoscopic instruments. Minim.Invasive.Ther.Allied Technol. 2001 May;10(3):145-54.

150. Helling TS, Khandelwal A. The challenges of resident training in complex hepatic, pancreatic, and biliary procedures. J.Gastrointest.Surg. 2008 Jan;12(1):153-8.

151. Fosse E, Elle OJ, Samset E, Johansen M, Rotnes JS, Tonnessen TI, Edwin B. [Image guided and robotic treatment--the advance of cybernetics in clinical medicine]. Tidsskr.Nor Laegeforen. 2000 Jan 10;120(1):65-9.

152. Lango T, Tangen GA, Marvik R, Ystgaard B, Yavuz Y, Kaspersen JH, Solberg OV, Hernes TA. Navigation in laparoscopy--prototype research platform for improved image-guided surgery. Minim.Invasive.Ther.Allied Technol. 2008;17(1):17-33.

153. Lamata P, Jalote-Parmar A, Lamata F, Declerck J. The Resection Map, a proposal for intraoperativehepatectomy guidance. Int J CARS 2008;3:299-306.

154. Tichansky DS, Taddeucci RJ, Harper J, Madan AK. Minimally invasive surgery fellows would perform a wider variety of cases in their "ideal" fellowship. Surg.Endosc. 2008 Mar;22(3):650-4.

155. Goetghebeur E, Loeys T. Beyond intention to treat. Epidemiol.Rev. 2002;24(1):85-90.

156. Porta N, Bonet C, Cobo E. Discordance between reported intention-to-treat and per protocol analyses. J Clin.Epidemiol. 2007 Jul;60(7):663-9.

157. Zakaria S, Donohue JH, Que FG, Farnell MB, Schleck CD, Ilstrup DM, Nagorney DM. Hepatic resection for colorectal metastases: value for risk scoring systems? Ann.Surg. 2007 Aug;246(2):183-91.

158. Chiappa A, Makuuchi M, Lygidakis NJ, Zbar AP, Chong G, Bertani E, Sitzler PJ, Biffi R, Pace U, Bianchi PP, et al. The management of colorectal liver metastases: Expanding the role of hepatic resection in the age of multimodal therapy. Crit Rev.Oncol.Hematol. 2009 Oct;72(1):65-75.

159. Jones OM, Rees M, John TG, Bygrave S, Plant G. Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival after liver resection. Br.J Surg. 2005 Sep;92(9):1165-8.

160. Grobmyer SR, Fong Y, D'Angelica M, Dematteo RP, Blumgart LH, Jarnagin WR. Diagnostic laparoscopy prior to planned hepatic resection for colorectal metastases. Arch.Surg. 2004 Dec;139(12):1326-30.

161. Karoui M, Penna C, min-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann.Surg. 2006 Jan;243(1):1-7.

162. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. Ann.Surg. 2005 Oct;242(4):540-4.

163. Andres A, Majno PE, Morel P, Rubbia-Brandt L, Giostra E, Gervaz P, Terraz S, Allal AS, Roth AD, Mentha G. Improved long-term outcome of surgery for advanced colorectal liver metastases: reasons and implications for management on the basis of a severity score. Ann.Surg.Oncol. 2008 Jan;15(1):134-43.

164. Mala T, Bohler G, Mathisen O, Bergan A, Soreide O. Hepatic resection for colorectal metastases: can preoperative scoring predict patient outcome? World J.Surg. 2002 Nov;26(11):1348-53.

165. Panis Y, Ribeiro J, Chretien Y, Nordlinger B. Dormant liver metastases: an experimental study. Br.J Surg. 1992 Mar;79(3):221-3.

166. Burpee SE, Kurian M, Murakame Y, Benevides S, Gagner M. The metabolic and immune response to laparoscopic versus open liver resection. Surg.Endosc. 2002 Jun;16(6):899-904.

167. Van den EM, Hendlisz A. Treatment of colorectal liver metastases: a review. Rev.Recent Clin.Trials 2009 Jan;4(1):56-62.

168. Nagakura S, Shirai Y, Yokoyama N, Wakai T, Suda T, Hatakeyama K. Major hepatic resection reduces the probability of intrahepatic recurrences following resection of colorectal carcinoma liver metastases. Hepatogastroenterology 2003 May;50(51):779-83.

169. Cho YB, Lee KU, Lee HW, Cho EH, Yang SH, Cho JY, Yi NJ, Suh KS. Anatomic versus non-anatomic resection for small single hepatocellular carcinomas. Hepatogastroenterology 2007 Sep;54(78):1766-9.

170. Guzzetti E, Pulitano C, Catena M, Arru M, Ratti F, Finazzi R, Aldrighetti L, Ferla G. Impact of type of liver resection on the outcome of colorectal liver metastases: a case-matched analysis. J.Surg.Oncol. 2008 May 1;97(6):503-7.

171. Zorzi D, Mullen JT, Abdalla EK, Pawlik TM, Andres A, Muratore A, Curley SA, Mentha G, Capussotti L, Vauthey JN. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. J.Gastrointest.Surg. 2006 Jan;10(1):86-94.

172. Nishio H, Hamady ZZ, Malik HZ, Fenwick S, Rajendra PK, Toogood GJ, Lodge JP. Outcome following repeat liver resection for colorectal liver metastases. Eur.J.Surg.Oncol. 2007 Aug;33(6):729-34.

173. Antoniou A, Lovegrove RE, Tilney HS, Heriot AG, John TG, Rees M, Tekkis PP, Welsh FK. Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases. Surgery 2007 Jan;141(1):9-18.

174. Lee BR, Tan BJ, Smith AD. Laparoscopic port site metastases: incidence, risk factors, and potential preventive measures. Urology 2005 Apr;65(4):639-44.

175. Vigano L, Ferrero A, Lo TR, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. Ann.Surg.Oncol. 2008 Sep;15(9):2458-64.

176. Dagher I, Proske JM, Carloni A, Richa H, Tranchart H, Franco D. Laparoscopic liver resection: results for 70 patients. Surg.Endosc. 2007 Apr;21(4):619-24.

177. Sandler A, Kimura K, Soper R. Nonanatomic hepatic resection with a pledgetted suturing technique. J Pediatr.Surg 2001 Jan;36(1):209-12.

178. Lamata P, Lamata F, Sojar V, Makowski P, Massoptier L, Casciaro S, Ali W, Studeli T, Declerck J, Elle OJ, et al. Use of the Resection Map system as guidance during hepatectomy. Surg Endosc 2010 Feb 23.

179. Teramoto K, Kawamura T, Takamatsu S, Noguchi N, Nakamura N, Arii S. Laparoscopic and thoracoscopic partial hepatectomy for hepatocellular carcinoma. World J Surg. 2003 Oct;27(10):1131-6.

180. Huang MT, Wei PL, Wang W, Li CJ, Lee YC, Wu CH. A series of laparoscopic liver resections with or without HALS in patients with hepatic tumors. J Gastrointest.Surg. 2009 May;13(5):896-906.

181. Tsuchiya M, Otsuka Y, Tamura A, Nitta H, Sasaki A, Wakabayashi G, Kaneko H. Status of endoscopic liver surgery in Japan: a questionnaire survey conducted by the Japanese Endoscopic Liver Surgery Study Group. J Hepatobiliary.Pancreat.Surg 2009;16(4):405-9.

182. Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S, Wakabayashi G. Ten-year experience of totally laparoscopic liver resection in a single institution. Br.J Surg 2009 Mar;96(3):274-9.

183. Poultsides G, Brown M, Orlando R, III. Hand-assisted laparoscopic management of liver tumors. Surg.Endosc. 2007 Aug;21(8):1275-9.

184. Robles R, Marin C, Abellan B, Lopez A, Pastor P, Parrilla P. A new approach to hand-assisted laparoscopic liver surgery. Surg.Endosc. 2008 Mar 6.

185. Dulucq JL, Wintringer P, Stabilini C, Berticelli J, Mahajna A. Laparoscopic liver resections: a single center experience. Surg Endosc 2005 Jul;19(7):886-91.

186. Mala T, Edwin B, Gladhaug I, Fosse E, Soreide O, Bergan A, Mathisen O. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. Surg.Endosc. 2002 Jul;16(7):1059-63.

187. Santambrogio R, Opocher E, Ceretti AP, Barabino M, Costa M, Leone S, Montorsi M. Impact of intraoperative ultrasonography in laparoscopic liver surgery. Surg.Endosc. 2007 Feb;21(2):181-8.

188. Voogt MJ, Trillaud H, Kim YS, Mali WP, Barkhausen J, Bartels LW, Deckers R, Frulio N, Rhim H, Lim HK, et al. Volumetric feedback ablation of uterine fibroids using magnetic resonance-guided high intensity focused ultrasound therapy. Eur.Radiol. 2011 Sep 8.

189. Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran pathologic basis of disease. 8th ed. Philadelphia: Saunders Elsevier; 2010.: 1450 p.

190. Luo W, Zhou X, Yu M, He G, Zheng X, Li Q, Liu Q, Han Z, Zhang J, Qian Y. Ablation of high-intensity focused ultrasound assisted with SonoVue on Rabbit VX2 liver tumors: sequential findings with histopathology, immunohistochemistry, and enzyme histochemistry. Ann.Surg Oncol. 2009 Aug;16(8):2359-68.

191. Zervas NT, Kuwayama A. Pathological characteristics of experimental thermal lesions. Comparison of induction heating and radiofrequency electrocoagulation. J Neurosurg. 1972 Oct;37(4):418-22.

192. Moritz AR, Henriques FC. Studies of Thermal Injury: II. The Relative Importance of Time and Surface Temperature in the Causation of Cutaneous Burns. Am.J Pathol. 1947 Sep;23(5):695-720.

193. Ozaki T, Mori I, Nakamura M, Utsunomiya H, Tabuse K, Kakudo K. Microwave cell death: Immunohistochemical and enzyme histochemical evaluation. Pathol.Int. 2003 Oct;53(10):686-92.

194. Nikfarjam M, Muralidharan V, Christophi C. Mechanisms of focal heat destruction of liver tumors 1. J Surg Res. 2005 Aug;127(2):208-23.

195. Braga L, Semelka RC. Magnetic resonance imaging features of focal liver lesions after intervention. Top.Magn Reson.Imaging 2005 Feb;16(1):99-106.

196. Low RN. MR imaging of the liver using gadolinium chelates. Magn Reson.Imaging Clin.N.Am. 2001 Nov;9(4):717-43.

197. Cizginer S, Tatli S, Hurwitz S, Tuncali K, vanSonnenberg E, Silverman SG. Biochemical and hematologic changes after percutaneous radiofrequency ablation of liver tumors: experience in 83 procedures. J Vasc.Interv.Radiol. 2011 Apr;22(4):471-8.

198. Vanagas T, Gulbinas A, Pundzius J, Barauskas G. Radiofrequency ablation of liver tumors (I): biological background. Medicina (Kaunas.) 2010;46(1):13-7.

199. Jarnagin WR, Blumgart LH. Blumgard's surgery of the liver, biliary tract and pancreas. 5th edition ed. Philadelphia, PA: Saunders Elsevier; 2012.-2080 p.

12. ERRATA

Paper 1:

- It should be 176 instead of 177 (page 34, section “Patients” of the abstract, line 2; and page 36, subsection “Intraoperative results” of section “Results”).
- It should be “115 Cases of single resection” instead of “114 Cases of single resection”, “23 Cases of 2 concomitant resection” instead of “24 Cases of 2 concomitant resections” and “176 Laparoscopic liver resections” instead of “177 Laparoscopic liver resection” (page 36, Figure 2)

13. PAPERS

I

II

III

IV

Surg Endosc (2011) 25:3881–3889
DOI 10.1007/s00464-011-1815-x

Comparative evaluation of laparoscopic liver resection for posterosuperior and anterolateral segments

Airazat M. Kazaryan · Bård I. Røsok · Irina Pavlik Marangos · Arne R. Rosseland · Bjørn Edwin

Received: 27 May 2010 / Accepted: 9 June 2011 / Published online: 7 July 2011

Abstract

Background Totally laparoscopic liver resection of lesions located in the posterosuperior segments is reported to be technically challenging. This study aimed to define whether these technical difficulties affect the surgical outcome.

Methods A total of 220 patients underwent laparoscopic liver resection during 244 procedures from August 1998 to December 2010. The patients who underwent primary minor single liver resection for malignant tumors affecting either posterosuperior segments 1, 7, 8, and, 4a (group 1) or anterolateral segments 2, 3, 5, 6, and 4b (group 2) were included in the study. Seventy-five procedures found to be eligible for the study, including 28 patients in group 1 and 47 patients in group 2. Intraoperative unfavorable incidents were graded on the basis of the Satava approach and postoperative complications were graded in agreement with the Accordion classification.

Results The operative time (median, 127 min) and blood loss (median, 200 ml) were equivalent in the two groups. The rates for blood transfusions and intraoperative accidents did not differ statistically between the groups. A tumor-free margin resection was achieved in 94.7% of the procedures, equivalently in both groups. The postoperative course was similar in the two groups. Postoperative complications developed in 2 cases (7.1%) in group 1 and 2 cases (4.3%) in group 2 ($p = 0.626$). The median hospital stay was 2 days in both groups.

Conclusions Laparoscopic liver resection for lesions located in posterosuperior segments represents certain technical challenges. However, appropriate adjustment of surgical techniques and optimal patient positioning enables the laparoscopic technique to provide safe and effective parenchyma-sparing resections for lesions located in both posterosuperior and anterolateral segments.

Keywords Anterolateral segments · Laparoscopic liver resection · Posterosuperior segments

Presented at the 18th EAES Congress, June 16–19, 2010, Geneva, Switzerland.

A. M. Kazaryan (✉) · I. P. Marangos · B. Edwin
Interventional Centre, Rikshospitalet, Oslo University Hospital Health Trust, 0027 Oslo, Norway
e-mail: kazaryan@gmail.com

A. M. Kazaryan · B. I. Røsok · A. R. Rosseland · B. Edwin
Department of Gastrointestinal and Hepatobiliary Surgery, Rikshospitalet, Oslo University Hospital Health Trust, 0027 Oslo, Norway

A. M. Kazaryan · I. P. Marangos · B. Edwin
Institute of Clinical Medicine, Medical Faculty, University of Oslo, 0316 Oslo, Norway

A. M. Kazaryan
Surgical Department, Drammen Hospital, 3004 Vestre Viken Health Trust, Drammen, Norway

Treatment of pathologic liver lesions is a fast-developing area within current surgical practice [1]. In the early 1990s, Reich et al. [2] and Gagner et al. [3] reported the first cases of laparoscopic liver resection. Since that time, the feasibility and safety of this procedure have been documented in several reports [4–19]. Despite tremendous advancement in the field of laparoscopic hepatobiliary surgery related to both operative techniques and instrumentation, most laparoscopic liver resections still are mainly performed for easily accessible lesions [20].

Totally laparoscopic liver resection of posterosuperior segments are reported to be technically challenging [21]. Establishment of a good outcome after laparoscopic liver resection of lesions located in posterosuperior segments could stimulate a wider application of this patient friendly technique worldwide [22]. We aimed to define whether these technical difficulties affect clinical outcome in the expert hepatobiliary center.

Materials and methods

Patients

Rikshospitalet is a referral center for hepatobiliary procedures. A total of 220 patients underwent laparoscopic liver resection during 244 procedures from August 1998 to December 2010 at the Oslo University Hospital, Rikshospitalet. Our general experience and application of laparoscopic liver resections in the treatment of patients with colorectal liver metastases was reported earlier [14, 23].

Patients who underwent primary minor liver resection of malignant tumors affecting either posterosuperior segments 1, 7, 8, and 4a (group 1) or anterolateral segments 2, 3, 5, 6, and 4b (group 2) were included in this study (Fig. 1). To ensure an appropriate comparison between these two groups of interest, the study excluded patients with benign lesions; patients who underwent either hemihepatectomy, left lateral lobectomy, or combined liver ablation procedures; patients who simultaneously underwent another major laparoscopic operation; and patients with lesions affecting both anterolateral and posterosuperior segments. Seventy-five procedures were found to be eligible for the study, including 28 patients in group 1 and 47 patients in group 2.

The indications for laparoscopic liver resection were similar to those for open liver resection with respect to preoperative assessment of liver function, type of liver resection, and postoperative care. The majority of liver tumors in both groups were colorectal metastases (Table 1). The patient demographic data were similar in the two groups (Table 2).

We used unified criteria to grade perioperative adverse events. Intraoperative unfavorable incidents were graded on the basis of the Satava approach to surgical error evaluation (Table 3) and postoperative complications were graded in agreement with the Accordion classification (Clavien-Dindo-Strasberg classification) [23–27].

The standard preoperative investigations included liver imaging (spiral computed tomography [CT] and contrast ultrasonography as routine, and magnetic resonance imaging [MRI] and positron emission tomography [PET]-CT if required), chest imaging (plain X-ray or CT from 2005), and clinical biochemistry.

The patients received perioperative subcutaneous low-molecular-weight heparin. Intravenous anesthesia was used. At the beginning of surgery, bupivacaine hydrochloride was injected at the trocar port sites. Postoperative analgesia consisted of a nonsteroidal antiinflammatory drug and intravenous paracetamol. Intravenous opioids, mainly by means of patient-controlled analgesia pump, were given if additional analgesia was required. Postoperative opioid administration was registered from the first postoperative day. The patients were encouraged to mobilize early and resume feeding as soon as it was tolerated. Tumor size was measured after specimen fixation in formaldehyde during the histopathologic analyses of the resected specimens.

For patients discharged to a local hospital, information about the postoperative course was retrieved and incorporated into the analyses of morbidity and hospital stay.

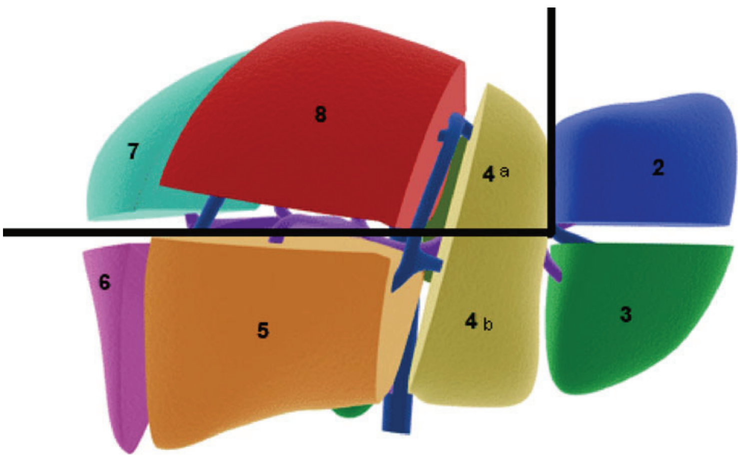


Fig. 1 Schematic view of liver segments. The *continuous black line* indicates a conventional division of the liver to posterosuperior segments 1, 7, 8, and 4a and anterolateral segments 2, 3, 5, 6, and 4b

Table 1 Representation of indications for surgery

	Group 1 ($n = 28$)	Group 2 ($n = 47$)	Total ($n = 75$)
Metastatic tumors	28	43	71
Colorectal adenocarcinoma	24	36	60
Anal squamous cell carcimoma	1	1	2
Pancreatic glucagonoma	1	–	1
Pancreatic adenocarcinoma	–	1	1
Lung adenocarcinoma	1	1	2
Melanoma (eye)	1	1	1
Carcinoid	–	2	1
Malignant hemangiopericytoma	–	1	1
Primary liver tumors:	–	4	4
Hepatocellular carcinoma	–	3	3
Cholangiocarcinoma	–	1	1

Table 2 Patient characteristics

Parameters	Group 1 ($n = 28$)	Group 2 ($n = 47$)	p Value	Total ($n = 75$)
Age: years (range)	68 (43–82)	62 (35–88)	0.155	65 (35–88)
ASA score: n (range)	2 (2–3)	3 (1–4)	0.111	2 (1–4)
Female/male	16/12	20/27	0.242	36/39
Previous laparotomy: n (%)	22 (78.6.1%)	39 (83.0%)	0.636	62 (82.7%)

Data are presented as median (range) or number (%)

Table 3 Grading of unfavorable intraoperative incidents on the basis of the Satava approach to surgical error evaluation; adapted for liver surgery

Grade	Definition of intraoperative incidents
1	Incidents managed without change of operative approach and without further consequences for the patient. It includes perforations of adherent or adjacent organs, minor change in intraoperative tactics, and cases with blood loss exceeding the normal range (corresponding to blood loss exceeding 1,000 ml in case of liver resection)
2	Incidents with further consequences for the patient. It includes cases requiring limited resection of intraoperatively injured organs or cases with blood loss appreciably more than the normal range. (It corresponds to blood loss exceeding 2,000 ml in case of liver resection). It also includes cases requiring conversion to an open approach
3	Incident leading to significant consequences for the patient

Perioperative mortality was defined as death within 30 days or before hospital discharge.

Techniques

The extent of liver resection was not altered by the application of laparoscopic techniques. The surgical technique has been described in detail previously [14].

To reach the most problematic segments (7 and 8), four laparoscopic port sites usually were needed (Fig. 2). The patient's right abdominal side was elevated up to between 45° and 60°. Usually, 12-mm port sites were used to enable application of a wide range of laparoscopic instruments and devices. Patient positioning and trocar placement should be carefully adjusted to the tumor location and patient constitution.

The first port site was established by Edwin's techniques on the pararectal line 10 cm below the costal arch [28]. This port site was applied as the main site for a 30° laparoscope. In very difficult cases (e.g., when the quality of the liver parenchyma prevented adequate mobilization of the right lobe), a flexible laparoscope (HD EndoEYE LTF-VH; Olympus, Tokyo, Japan) was used.

After a concise evaluation of the abdominal wall in the area of the intended trocar placement, two other trocars were established lateral to the initial port site. The most lateral trocar was positioned immediately anterior to the right paracolic line to ensure a maximal posterior approach. These port sites were applied as main sites for the surgical handling of instruments. One additional port site was established in the medioclavicular line about 5 cm below the costal arch. This site was used mainly for variable

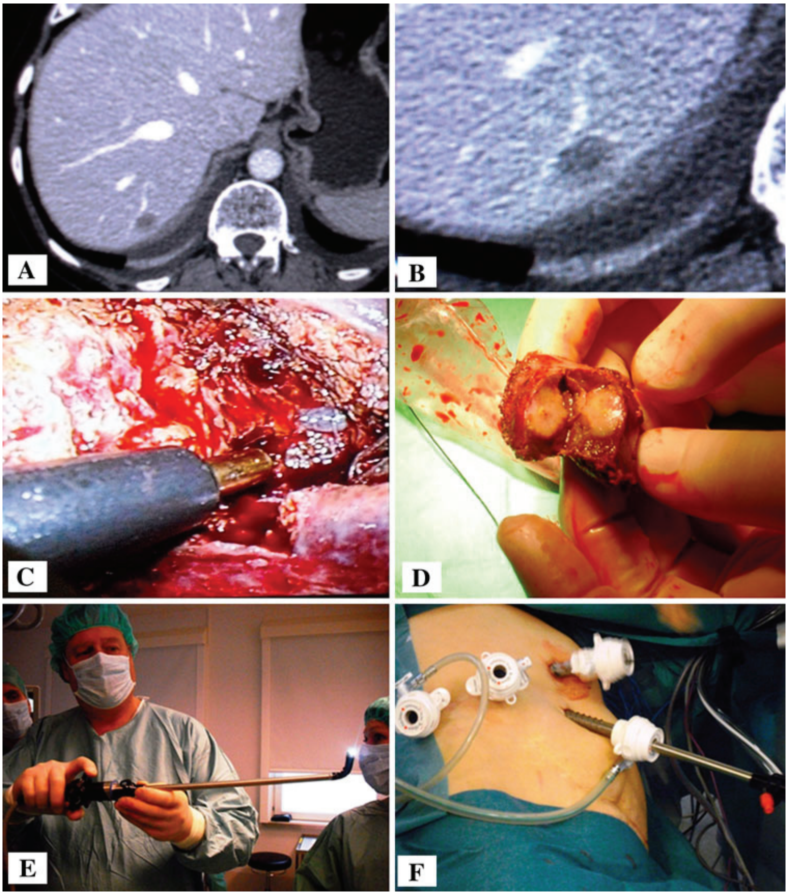


Fig. 2 Approach to segment 8. **A**, **B** Computed tomography of a tumor in segment 8 with a vein branch in proximity requiring attention. **C** Dissection. **D** Extracted specimen resulting from parenchyma-sparing resection. **E** Flexible laparoscope. **F** Trocar positioning

application of a five-blade liver retractor or for division of the anterior portion of the coronary ligament.

After division of adhesions due to previous abdominal surgery, the liver was thoroughly examined using laparoscopic ultrasonography with Doppler function. For exposure of lateral lesions in segment 8 and all lesions in segment 7, the posterior portion of the right lobe was fully mobilized. The right liver was lifted anteriorly by the liver retractor, and both the right triangular ligament and the coronary ligament were properly divided. The right liver was meticulously dissected away from the caval vein upward to the right hepatic vein (approach to segments 7 and 8), and in selected cases, the middle hepatic vein (in case of approach to lesions in the most cranial part of segment 8) were visualized.

The short hepatic veins were transected by clips or Ligasure (Covidien, Norwalk, CT, USA). The resected liver was removed in one piece through an enlarged umbilical port incision using a 15-mm pouch (EndoCatch; U.S. Surgical Corporation, Norwalk, CT, USA).

Statistical analysis

The major treatment outcomes were compared between groups 1 and 2. The data are presented as median (range) or number (percentage). Fisher's exact test or Pearson's chi-square test was applied to compare proportions between groups as appropriate. For comparison of continuous variables, the Mann–Whitney *U* test was used.

The overall survival for patients with colorectal liver metastases was evaluated. The log-rank test was applied for comparison of survival between groups.

The median follow-up period was 18 months (range, 6–56 months) in group 1 and 26 months (range, 5–121 months) in group 2 ($p = 0.176$). Follow up status (i.e., patient survival and tumor recurrence in the liver) was finally verified in May 2011.

Results

No conversions to open surgery occurred in either of the studied groups. The types of resections are presented in Table 4.

The operative time and blood loss were equivalent in the two groups (Table 5). The rate of blood transfusions and unfavorable intraoperative accidents did not differ statistically between the groups. One intraoperative accident occurred in group 1: a case of immoderate intraoperative bleeding (1,700 ml, managed laparoscopically) in a patient with colorectal metastasis in segment 8 (Satava grade 1). Three intraoperative accidents occurred in group 2: a case of minor perforation to the small bowel during surgery (immediately sutured laparoscopically) in a patient with colorectal metastasis in segments 5 and 6 (Satava grade 1), a case of immoderate intraoperative bleeding (2,000 ml, managed laparoscopically) in a patient with colorectal metastasis in segments 5 and 4b (Satava grade 1), and a case of immoderate intraoperative bleeding (2,500 ml, managed laparoscopically) in a patient with liver cirrhosis and hepatocellular carcinoma in segments 2 and 3 (Satava grade 2). Neither of the groups had perioperative mortality.

The median tumor size was similar in the two groups. No significant difference in weight or dimensions of the resected liver specimen was observed. Two cases in each group had involvement of tumor tissue in the resection. For one additional case in each group, the resection margin was negative but less than 1 mm. A tumor-free margin resection was achieved totally in 94.7% of the procedures of both groups (Table 6). The minimal distance from the resection line to the tumor tissue was significantly shorter in group 1 (median, 3 mm) than in group 2 (median, 8 mm).

Table 4 Representation of resection types

Segments	No. of cases
Group 1 ($n = 28$)	
7	13
8	7
4a	3
1	2
7 and 8	2
7, 8, and 4a	1
Group 2 ($n = 47$)	
3	11
6	11
5	5
4b	5
2	3
5 and 6	5
5 and 4b	4
2 and 3	2
3 and 4b	1

The postoperative course did not differ statistically between the studied groups (Table 5). On the day of the operation, 70 (93.3%) of the 75 patients began to drink (26 of the 28 patients in group 1 and 44 of the 47 patients in group 2). All the patients in both groups started to consume a solid diet on the first postoperative day. All the patients were transferred from the postoperative intensive care unit to the ordinary patient ward on the day of the operation. Only 14 (50%) of the 28 patients in group 1 and 21 (44.7%) of the 47 patients in group 2 required postoperative opioid administration.

Two postoperative complications (7.1%) developed in group 1: biliary leakage managed by percutaneous drainage in a patient with colorectal metastasis in segments 7, 8, and 4a (readmitted for development of abscess, treated by antibiotics) and liver abscess in the area of liver resection managed by percutaneous drainage in a patient with pancreatic glucagonoma in segment 4a. Two complications (6.4%) developed in group 2: bleeding at a trocar site of a patient with colorectal metastasis in segment 3 controlled by suture with the patient under local anesthesia and pneumonia and intraabdominal seroma (percutaneously drained) in a patient with colorectal metastasis in segments 5 and 4b.

In an additional case, diagnostic laparoscopy was applied on postoperative day 2 due to unconfirmed suspicion (occasioned by a sharp rise in C-reactive protein) of biliary leakage in a patient with metastasis of anal squamous cell carcinoma. The patient recovered uneventfully and was discharged on postoperative day 5. All postoperative complications corresponded to grade 3 of the Accordion classification.

The median postoperative hospital stay was 2 days in both groups. Of the 75 patients, 68 (90.7%) were discharged to their private homes (25 of the 28 patients in group 1 and 43 of the 47 patients in group 2), whereas a smaller number were transferred to a local hospital, another hospital department, or a patient hotel for convalescence.

Tumor recurrence in the liver developed in 8 (28.6 %) of the 28 patients in group 1 after a median of 7 months (range, 4–8 months), and in 16 (34%) of the 47 patients in group 2 after a median of 7 months (range, 2–25 months). The data on postoperative liver recurrence and overall survival did not differ statistically between the two groups ($p = 1.000$ and 0.332 respectively).

Table 5 Surgical outcomes

	Group 1 ($n = 28$)	Group 2 ($n = 47$)	p Value	Total ($n = 75$)
Intraoperative parameters				
Intraoperative incidents: n (%)	1 (3.6)	3 (6.4)	1.000	4 (5.3)
Operative time: min (range)	125 (50–336)	130 (50–315)	0.891	127 (50–336)
Blood loss: ml (range)	200 (<50–1,700)	200 (<50–2,500)	0.849	200 (<50–2,500)
Blood transfusions	1 (3.6)	4 (8.5)	0.645	5 (6.7)
Postoperative parameters: n (%)				
Postoperative complications: n (%)	2 (7.1%)	2 (4.3)	0.626	4 (5.3)
Postoperative first oral intake of fluids: postoperative day (range)	0 (0–1)	0 (0–1)	0.899	0 (0–1)
Postoperative first oral intake of solid food: postoperative day (range)	1 (0–1)	1 (0–1)	0.128	1 (0–1)
Postoperative opioid requirements: days (range)	0.5 (0–3)	0 (0–2)	0.849	0 (0–3)
Postoperative stay: days (range)	2 (1–9)	2 (1–7)	0.551	2 (1–9)

Data are presented as median (range) or number (%)

Table 6 Histopathologic data[a]

Parameter	Group 1 ($n = 28$)	Group 2 ($n = 47$)	p Value	Total ($n = 75$)
Tumor-free margin resection: n (%)	26 (92.9)	45 (95.7)	0.626	53 (94.7)
Minimal distance from resection line to tumor tissue: mm (range)	3 (0–13)	8 (0–30)	0.003	5 (0–30)
Largest tumor size: mm (range)	24 (6–80)	25 (7–75)	0.549	25 (6–80)
Weight of resected specimen: g (range)	38 (5–174)	52 (7–270)	0.635	44 (5–270)
Largest dimension of resectat: mm (range)	60 (25–90)	65 (25–120)	0.359	63 (25–120)

[a] Data are presented as median (range) or number (%)

Discussion

Video laparoscopy has greatly changed the practice of contemporary surgery, conferring several benefits including minimal damage to the abdominal wall, faster recovery, fewer wound complications, and improved cosmetic results. Despite early skepticism concerning laparoscopic liver resection, it currently is accepted generally as a feasible alternative to open resection, also for cancer [29–31].

The current study demonstrated that laparoscopic liver resection can be performed safely for lesions located in both the anterolateral and posterosuperior segments by an experienced surgical team. We had a low rate of perioperative adverse events (a 5.3% rate for intraoperative unfavorable accidents by the Satava approach and a 5.3% rate for postoperative complications by the Accordion classification), and no conversion or mortality occurred in the analyzed groups.

Despite their relatively early introduction in 1992, laparoscopic techniques in liver surgery have not spread worldwide as broadly as, for example, laparoscopy for cholecystectomy [29, 30]. The majority of hepatobiliary centers perform only open surgery for liver lesions. In centers performing laparoscopic liver resection, operations for lesions located in posterosuperior segments, which considered to be so-called “difficult segments”, are largely retained for open surgery.

For tumors located in segments 7 or 8, nonanatomic liver resection or right posterior sectionectomy is preferable to right hemihepatectomy because it preserves the liver parenchyma. However, these procedures are more challenging technically. Although only a small volume of liver parenchyma usually is removed in a nonanatomic liver resection, these resections in segments 7 and 8 are technically difficult because exposure of deeply located lesions is intricate, and the transection plane can be rounded or angled [9, 19, 32]. Hanging techniques implying mobilization of the right liver lobe and dissection along the caval vein and up between the orifice of the right and the middle hepatic veins enabling to hang the right liver lobe could be of major assistance (personal communication, Dr. I. S.Tait, Dundee, UK).

In our series, the laparoscopic approach to posterosuperior segments was not associated with significant difficulties or increased morbidity. This perception is supported equally by both intra- and postoperative outcomes for resections of anterolateral and posterosuperior liver segments. Appropriate adjustment of trocar placement, a flexible laparoscope, extensive mobilization of the right liver lobe, and adequate use of the gravity force are of great help in such cases. In our experience, the availability of several high-resolution large monitors in the operative theater enabling surgeons to view not only intraoperative

Fig. 3 Operative room environment. **A** Imaging with preoperative computed tomography. **B** Imaging with three-dimensional liver reconstruction

ultrasonography but also preoperative imaging including three-dimensional reconstruction of crucial anatomic structures (vessels and bile ducts) was of major help (Fig. 3). This further perks up intraoperative navigation and thus may play an important role in laparoscopic liver surgery, especially in the case of tumors located in posterosuperior segments [33, 34].

The minimal distance from resection line to tumor tissue was the only parameter that differed significantly between the studied groups. With regard to malignant liver lesions, we have always aimed to achieve resection with a sufficiently safe resection margin with respect to tumor location. However, the observed phenomenon may occur due to a poorer exposition of the operative field during the approach to tumors located in posterosuperior segments. This has led to increased concern with regard to possible vascular or biliary injury. Thus, the surgeon was constrained to perform resection closer to the tumor margin to prevent the additional risk while retaining a secure free margin.

In our series, this phenomenon did not lead to a higher rate of tumor-involved resection margins, to a higher rate of recurrence in the liver, or to a poorer survival in patients with resections of lesions located in posterosuperior segments.

Thoracoscopic access to approach segments 7 and 8 is suggested [35]. The thoracoscopic approach is associated with a longer operative time and opening of the thoracic cavity, consequently leading to increased risk of complications [36, 37]. This could indicate that application of the thoracoscopic approach is not impeccable. A recent publication from Japan stated that the authors had switched from the thoracoscopic to the laparoscopic approach for resection of lesions in segment 8 due to lack of appreciable benefits [38].

We used a totally laparoscopic rather than a hand-assisted approach as used by many others [39, 40]. With some other surgeons, we believe that the hand-assisted method or hybrid techniques have a limited role [9]. These techniques supply a tactile sensation that is lacking during laparoscopy. However, this approach requires a larger incision, which reduces the benefits of minimally invasive surgery. Besides, fatigue in the inserted hand and air leakage represent drawbacks of the hand-assisted method [41]. However a handport could be applied in very challenging situations and tumor locations when the surgeon does not achieve significant progress in the procedure or feels himself not fully confident without tactile control of resection.

The hand-assisted technique was applied in only two cases to facilitate extra-challenging resections in group 1 (7.1%). None of the cases in group 2 required use of the hand-assisted technique. The decision to establish a handport was made during the procedure based on intraprocedural circumstances to reduce an expected unreasonably long operative time in case of application of the totally laparoscopic approach. The handport was established before liver mobilization in one case and after liver mobilization in another case.

Intraoperative ultrasonography could partly substitute for the lacking tactile sensation during totally laparoscopic resection. Therefore, its application during laparoscopic liver resection is mandatory to ensure adequate tumor identification and margin control [42, 43].

Theoretical premises and experimental studies have led to anxiety among clinicians concerning the potential risk for gas embolism during laparoscopic liver resection, which has been especially highlighted with regard to posterosuperior segments. This argument also has been used by supporters of hand-assisted techniques [44, 45]. However accumulated world experience has shown that this risk has been greatly overestimated [46, 47].

As for open surgery, bleeding and biliary leakage were regarded as the most serious complications in both groups [48]. However, high-tech surgical equipment has considerably contributed to reducing the hazard of such complications [49]. We experienced adequate hemostatic control by means of modern surgical equipment in both patient groups. The postoperative course was equal in the two groups. The median duration of postoperative stay was only 2 days. The vast majority of patients started to consume fluids on the day of the operation, and all the patients started to consume solid food on the first operative day in both groups.

Conclusion

Laparoscopic liver resection for lesions located in posterosuperior segments represents a certain technical challenge in contrast to anterolateral segments. However, appropriate adjustment of surgical techniques and patient positioning suited to the particular tumor location enables the laparoscopic technique to provide safe and effective parenchyma-sparing resections for lesions located in both posterosuperior and anterolateral segments. We recommend wide application of laparoscopic techniques for lesions located in posterosuperior segments for centers that have mastered laparoscopic liver resection of anterolateral segments with a high degree of confidence. This will enable provision of the best currently available treatment for a large number of patients, will favor parenchyma-sparing techniques, and will definitively contribute to further promotion of a patient-friendly concept of minimally invasive surgery.

Disclosures Airazat M. Kazaryan, Bård I. Røsok, Irina Pavlik Marangos, Arne R. Rosseland, and Bjørn Edwin have no conflicts of interest or financial ties to disclose.

References

1. Edwin B, Nordin A, Kazaryan AM (2011) Laparoscopic liver surgery: new frontiers. Scand J Surg 100:54–65
2. Reich H, McGlynn F, DeCaprio J, Budin R (1991) Laparoscopic excision of benign liver lesions. Obstet Gynecol 78(5 pt 2): 956–958
3. Gagner M, Rheault M, Dubuc J (1992) Laparoscopic partial hepatectomy for liver tumor. Surg Endosc 6:99
4. Azagra JS, Goergen M, Gilbart E, Jacobs D (1996) Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. Surg Endosc 10:758–761
5. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, Brock G, McMasters KM (2008) Experience with more than 500 minimally invasive hepatic procedures. Ann Surg 248:475–486
6. Cai XJ, Yang J, Yu H, Liang X, Wang YF, Zhu ZY, Peng SY (2008) Clinical study of laparoscopic versus open hepatectomy for malignant liver tumors. Surg Endosc 22:2350–2356
7. Chen HY, Juan CC, Ker CG (2008) Laparoscopic liver surgery for patients with hepatocellular carcinoma. Ann Surg Oncol 15: 800–806
8. Cherqui D, Husson E, Hammoud R, Malassagne B, Stephan F, Bensaid S, Rotman N, Fagniez PL (2000) Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 232: 753–762
9. Dagher I, Proske JM, Carloni A, Richa H, Tranchart H, Franco D (2007) Laparoscopic liver resection: results for 70 patients. Surg Endosc 21:619–624

10. Edwin B, Mala T, Gladhaug I, Fosse E, Mathisen Y, Bergan A, Soreide O (2001) Liver tumors and minimally invasive surgery: a feasibility study. J Laparoendosc Adv Surg Tech A 11:133–139
11. Gagner M, Rogula T, Selzer D (2004) Laparoscopic liver resection: benefits and controversies. Surg Clin North Am 84:451–462
12. Gayet B, Cavaliere D, Vibert E, Perniceni T, Levard H, Denet C, Christidis C, Blain A, Mal F (2007) Totally laparoscopic right hepatectomy. Am J Surg 194:685–689
13. Ito K, Ito H, Are C, Allen PJ, Fong Y, Dematteo RP, Jarnagin WR, D'Angelica MI (2009) Laparoscopic versus open liver resection: a matched-pair case control study. J Gastrointest Surg 13:2276–2283
14. Kazaryan AM, Pavlik MI, Rosseland AR, Rosok BI, Mala T, Villanger O, Mathisen O, Giercksky KE, Edwin B (2010) Laparoscopic liver resection for malignant and benign lesions: ten-year Norwegian single-center experience. Arch Surg 145:34–40
15. Koffron AJ, Auffenberg G, Kung R, Abecassis M (2007) Evaluation of 300 minimally invasive liver resections at a single institution: less is more. Ann Surg 246:385–392
16. Lee KF, Cheung YS, Chong CN, Tsang YY, Ng WW, Ling E, Wong J, Lai PB (2007) Laparoscopic versus open hepatectomy for liver tumours: a case control study. Hong Kong Med J 13:442–448
17. Mala T, Edwin B, Rosseland AR, Gladhaug I, Fosse E, Mathisen O (2005) Laparoscopic liver resection: experience of 53 procedures at a single center. J Hepatobiliary Pancreat Surg 12:298–303
18. Rau HG, Meyer G, Cohnert TU, Schardey HM, Jauch K, Schildberg FW (1995) Laparoscopic liver resection with the water-jet dissector. Surg Endosc 9:1009–1012
19. Vibert E, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B (2006) Laparoscopic liver resection. Br J Surg 93:67–72
20. Vigano L, Tayar C, Laurent A, Cherqui D (2009) Laparoscopic liver resection: a systematic review. J Hepatobiliary Pancreat Surg 16:410–421
21. Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez PL (2003) Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg 138:763–769
22. Cho JY, Han HS, Yoon YS, Shin SH (2008) Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. Surgery 144:32–38
23. Kazaryan AM, Marangos IP, Rosok BI, Rosseland AR, Villanger O, Fosse E, Mathisen O, Edwin B (2010) Laparoscopic resection of colorectal liver metastases: surgical and long-term oncologic outcome. Ann Surg 252:1005–1012
24. Satava RM (2005) Identification and reduction of surgical error using simulation. Minim Invasive Ther Allied Technol 14:257–261
25. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 240:205–213
26. Strasberg SM, Linehan DC, Hawkins WG (2009) The accordion severity grading system of surgical complications. Ann Surg 250:177–186
27. Porembka MR, Hall BL, Hirbe M, Strasberg SM (2010) Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the American College of Surgeons National Surgical Quality Improvement Program. J Am Coll Surg 210:286–298
28. Edwin B, Rosseland AR, Færden AE, Størkson R, Reiertsen O, Trondsen E, Engen J (1995) Open technique in creating pneumoperitoneum. Scand J Gastroenterol 30(Suppl 209):17
29. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS et al (2009) The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 250:825–830
30. Marvin MR, Buell JF (2009) Laparoscopic liver surgery. Adv Surg 43:159–173
31. Nguyen KT, Gamblin TC, Geller DA (2008) Laparoscopic liver resection for cancer. Future Oncol 4:661–670
32. Sandler A, Kimura K, Soper R (2001) Nonanatomic hepatic resection with a pledgetted suturing technique. J Pediatr Surg 36:209–212
33. Lamata P, Lamata F, Sojar V, Makowski P, Massoptier L, Casciaro S, Ali W, Studeli T, Declerck J, Elle OJ, et al (2010) Use of the Resection Map System as guidance during hepatectomy. Surg Endosc 24:2327–2337
34. Lango T, Tangen GA, Marvik R, Ystgaard B, Yavuz Y, Kaspersen JH, Solberg OV, Hernes TA (2008) Navigation in laparoscopy–prototype research platform for improved image-guided surgery. Minim Invasive Ther Allied Technol 17:17–33
35. Teramoto K, Kawamura T, Takamatsu S, Noguchi N, Nakamura N, Arii S (2003) Laparoscopic and thoracoscopic partial hepatectomy for hepatocellular carcinoma. World J Surg 27:1131–1136
36. Huang MT, Wei PL, Wang W, Li CJ, Lee YC, Wu CH (2009) A series of laparoscopic liver resections with or without HALS in patients with hepatic tumors. J Gastrointest Surg 13:896–906
37. Tsuchiya M, Otsuka Y, Tamura A, Nitta H, Sasaki A, Wakabayashi G, Kaneko H (2009) Status of endoscopic liver surgery in Japan: a questionnaire survey conducted by the Japanese Endoscopic Liver Surgery Study Group. J Hepatobiliary Pancreat Surg 16:405–409
38. Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S, Wakabayashi G (2009) Ten-year experience of totally laparoscopic liver resection in a single institution. Br J Surg 96:274–279
39. Poultsides G, Brown M, Orlando R III (2007) Hand-assisted laparoscopic management of liver tumors. Surg Endosc 21:1275–1279
40. Robles R, Marin C, Abellan B, Lopez A, Pastor P, Parrilla P (2008) A new approach to hand-assisted laparoscopic liver surgery. Surg Endosc 22:2357–2364
41. Dulucq JL, Wintringer P, Stabilini C, Berticelli J, Mahajna A (2005) Laparoscopic liver resections: a single-center experience. Surg Endosc 19:886–891
42. Mala T, Edwin B, Gladhaug I, Fosse E, Soreide O, Bergan A, Mathisen O (2002) A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. Surg Endosc 16:1059–1063
43. Santambrogio R, Opocher E, Ceretti AP, Barabino M, Costa M, Leone S, Montorsi M (2007) Impact of intraoperative ultrasonography in laparoscopic liver surgery. Surg Endosc 21:181–188
44. Jayaraman S, Khakhar A, Yang H, Bainbridge D, Quan D (2009) The association between central venous pressure, pneumoperitoneum, and venous carbon dioxide embolism in laparoscopic hepatectomy. Surg Endosc 23:2369–2373
45. Schmandra TC, Mierdl S, Hollander D, Hanisch E, Gutt C (2004) Risk of gas embolism in hand-assisted versus total laparoscopic hepatic resection. Surg Technol Int 12:137–143
46. Gagner M (2010) Small incision, big surgeon: laparoscopic liver resection for tumors without a doubt: Comment on "Laparoscopic Liver Resection for Malignant and Benign Lesions: Ten-Year Norwegian Single-Center Experience. Arch Surg 145:40–41
47. Nguyen KT, Gamblin TC, Geller DA (2009) World review of laparoscopic liver resection—2,804 patients. Ann Surg 250:831–841
48. Erdogan D, Busch OR, Gouma DJ, van Gulik TM (2009) Morbidity and mortality after liver resection for benign and malignant hepatobiliary lesions. Liver Int 29:175–180
49. Poon RT (2007) Current techniques of liver transection. HPB Oxford 9:166–173

V